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July 1951

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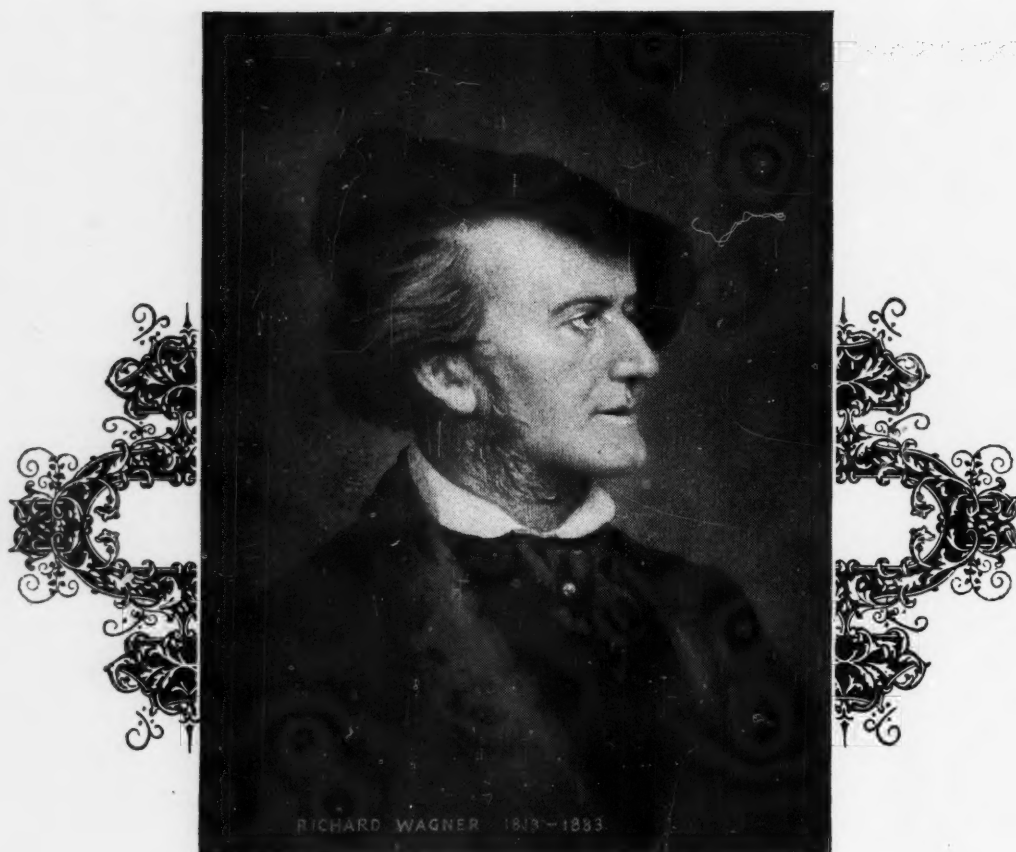
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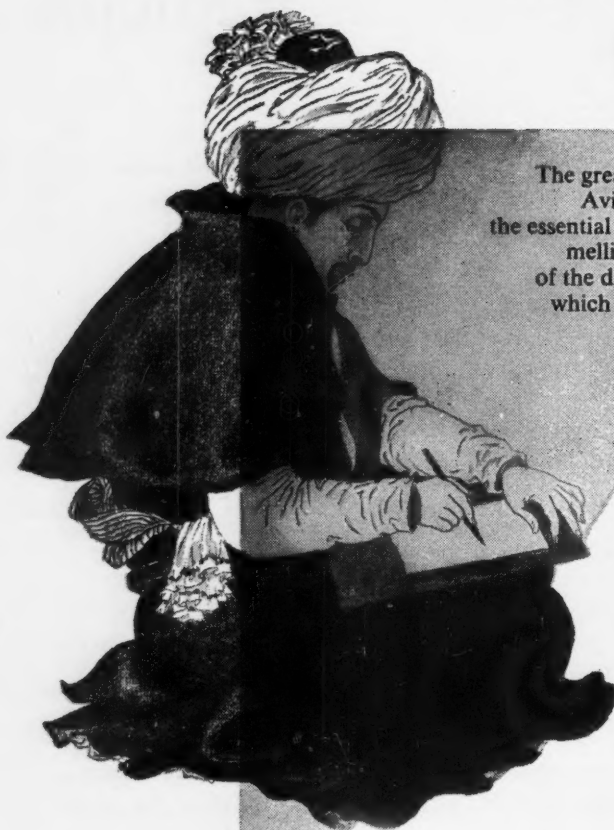
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for diagnosis

before symptoms occur...



The great Arab "prince of physicians," Avicenna (980-1037 A.D.), described the essential clinical features of diabetes mellitus. In his era, however, recognition of the disease was limited to cases in which morbidity was already manifest.

Early diagnosis of "pre-symptomatic" diabetes mellitus became feasible only centuries later, with the development of copper-reduction testing for glycosuria.

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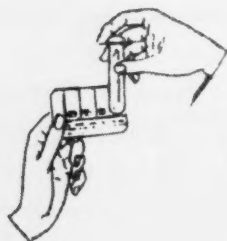
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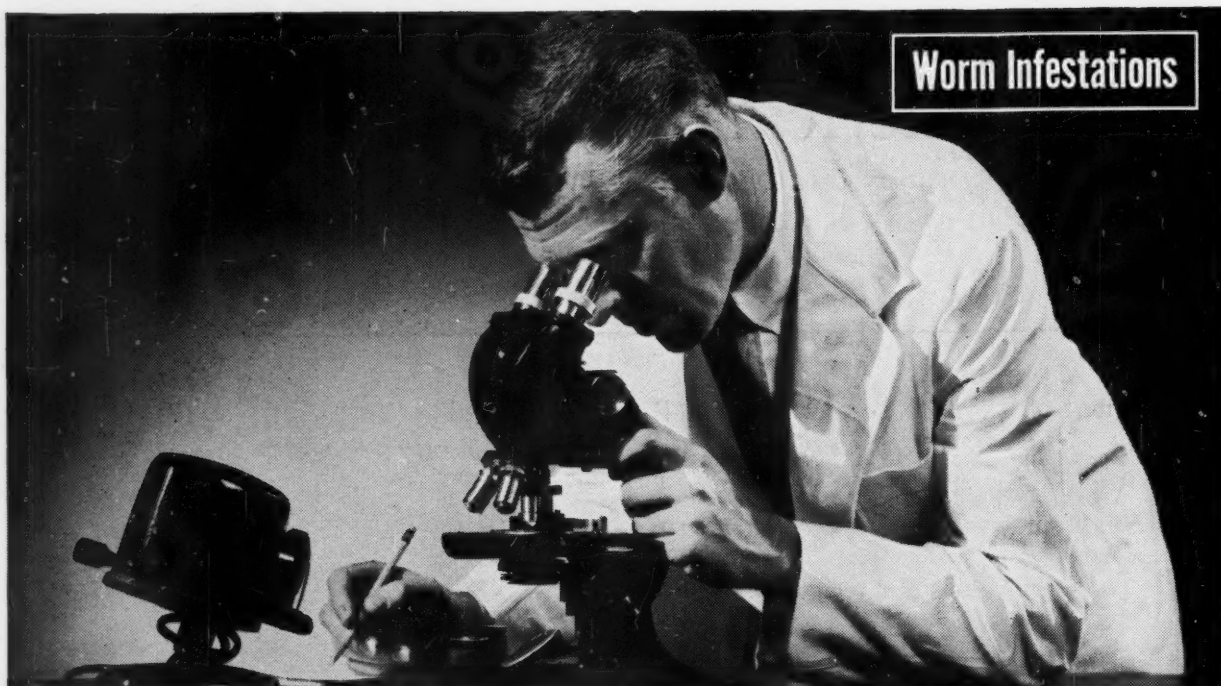
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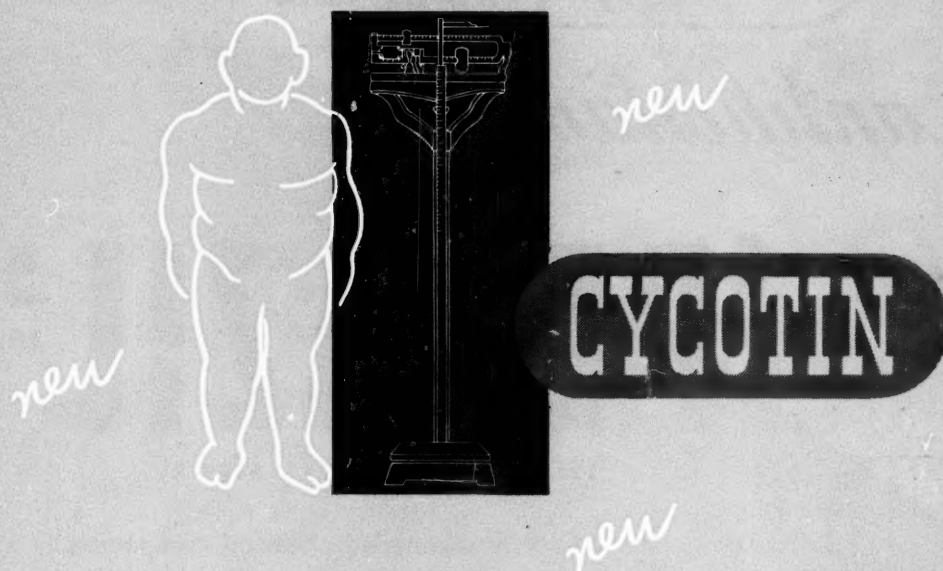
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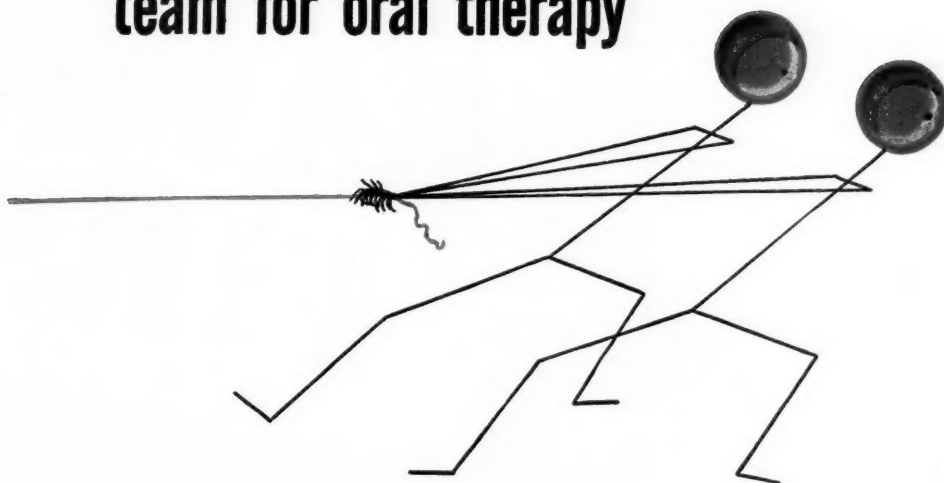
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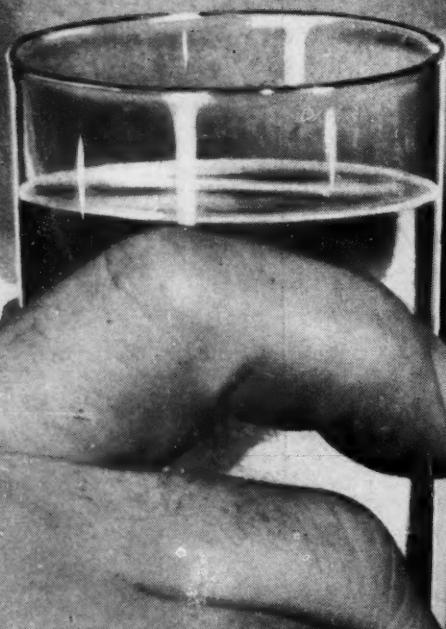
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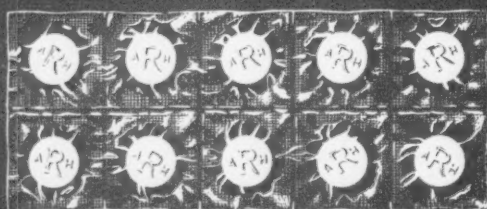
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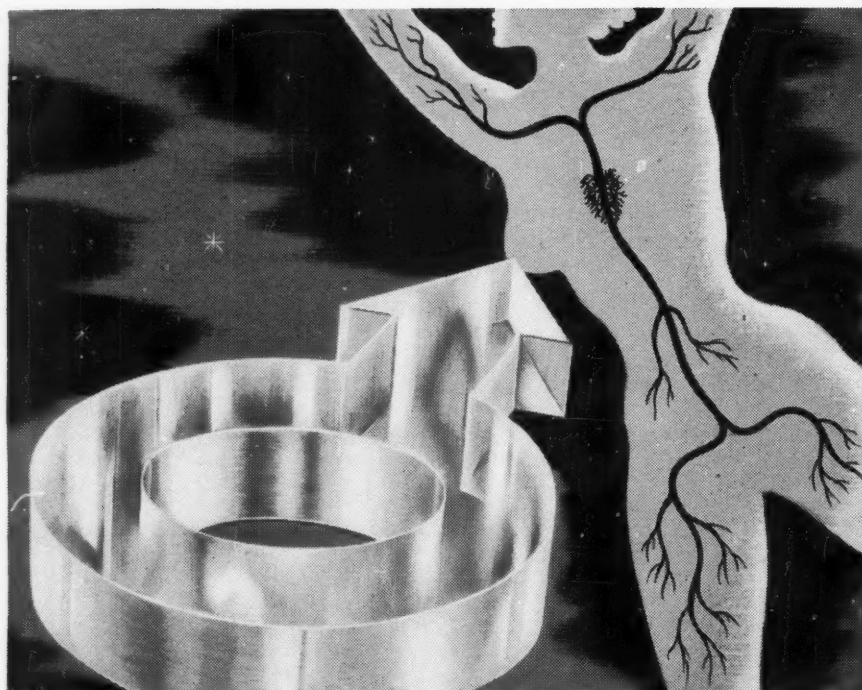


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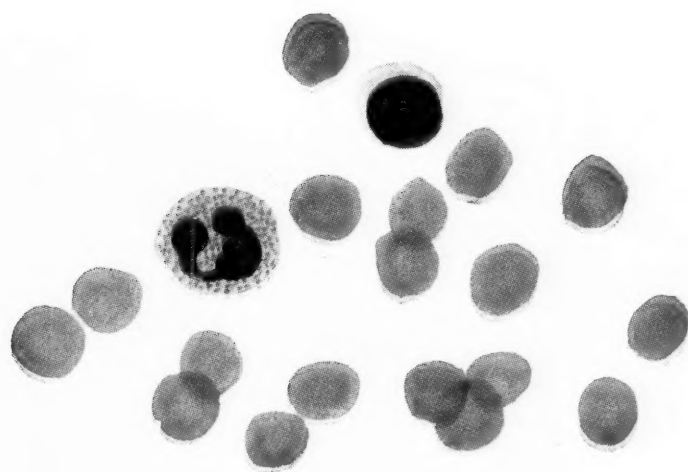
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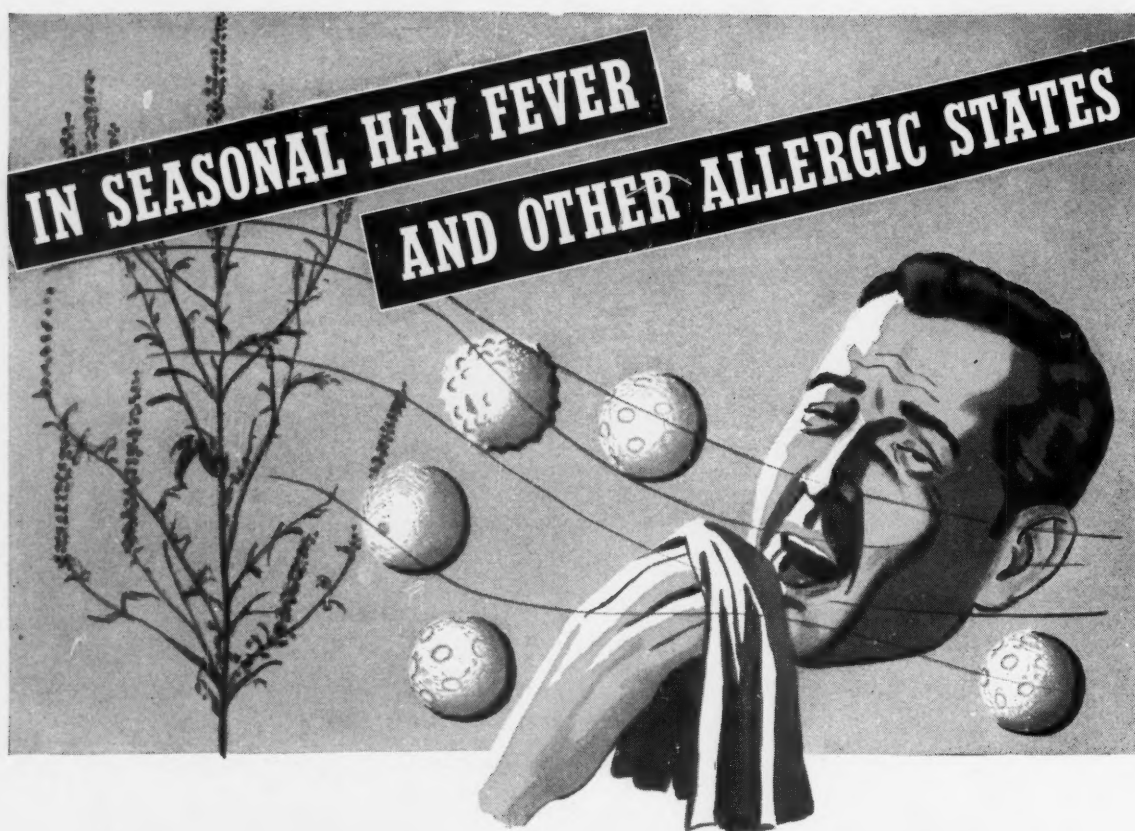
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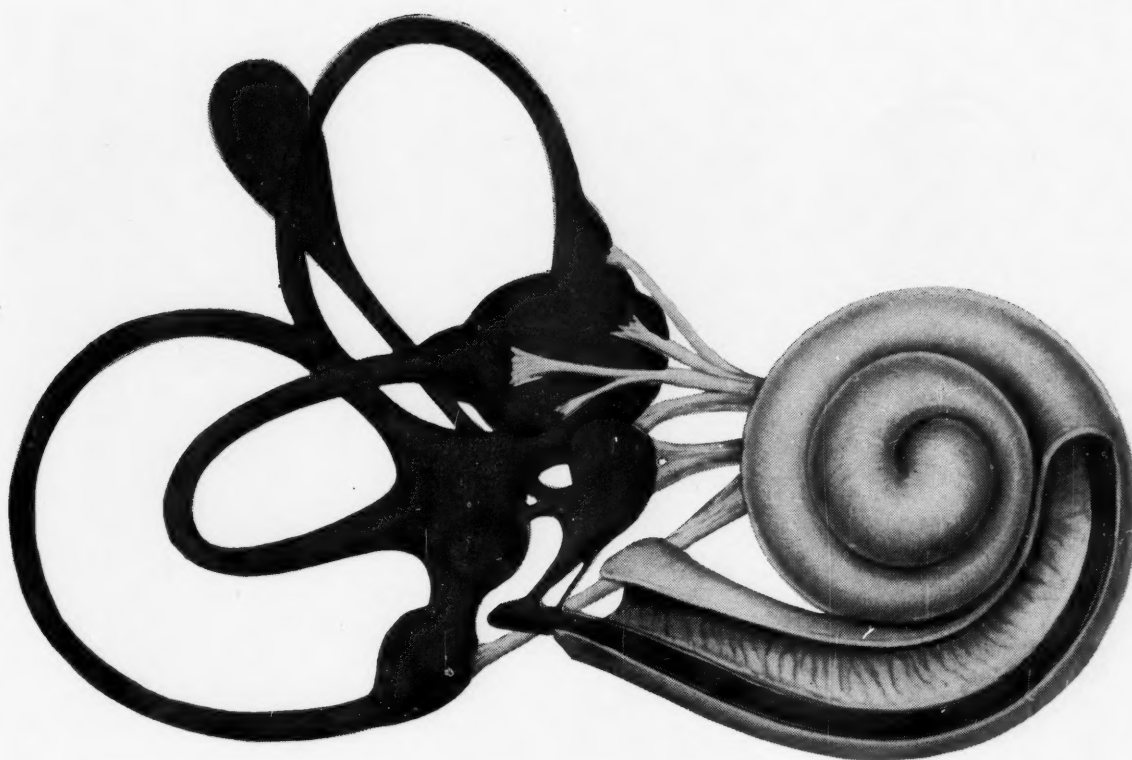
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—Tuttle, A. D.: *Special Breakdown of Case Histories*, presented at the Airlines Medical Directors Association Meeting, New York, N. Y., Aug. 28, 1949.

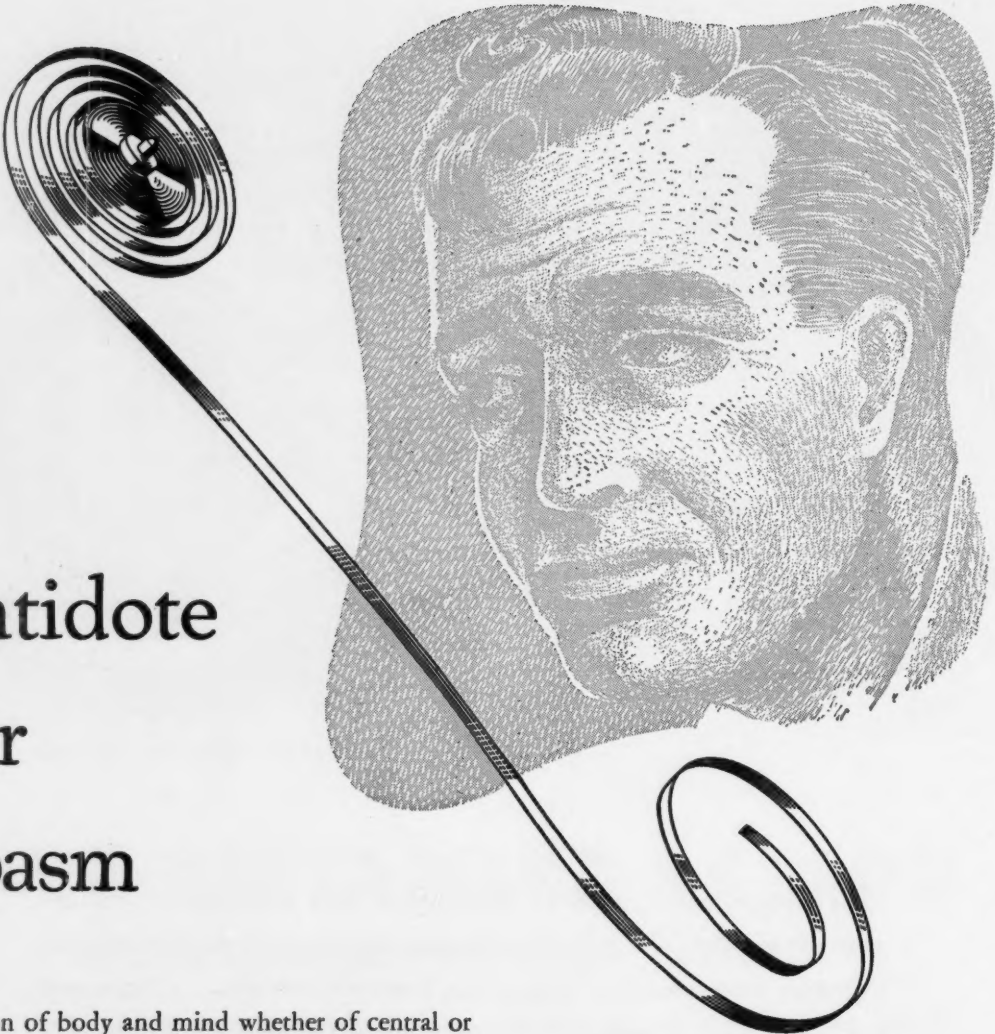
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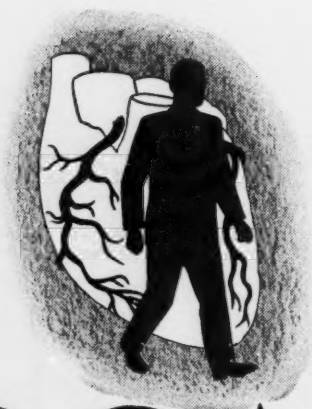
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**Gofman, J. W.
and Associates
Science 111:116
(1950)**

reference. Since the lay press (Saturday Evening Post, American Weekly and others) have discussed Gofman's paper at length, this concise material may prove helpful in correcting any misconceptions your patients may have gained from their reading.

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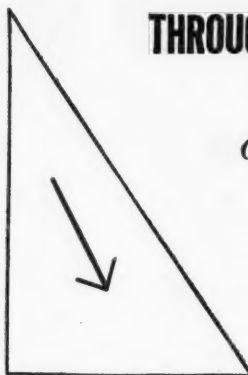
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*Kirwin, T. J., Lowsley, O. S., and Manning, J.: Effects of Pyridium in certain urogenital infections, *Am. J. Surg.* 62: 330-335, December 1943.

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$$\frac{S}{S-x} = KC$$

$$\frac{S}{S-x} - Ax = KC$$

$$\frac{a-x}{v} S = Ke \frac{A(S-x)}{S} x$$

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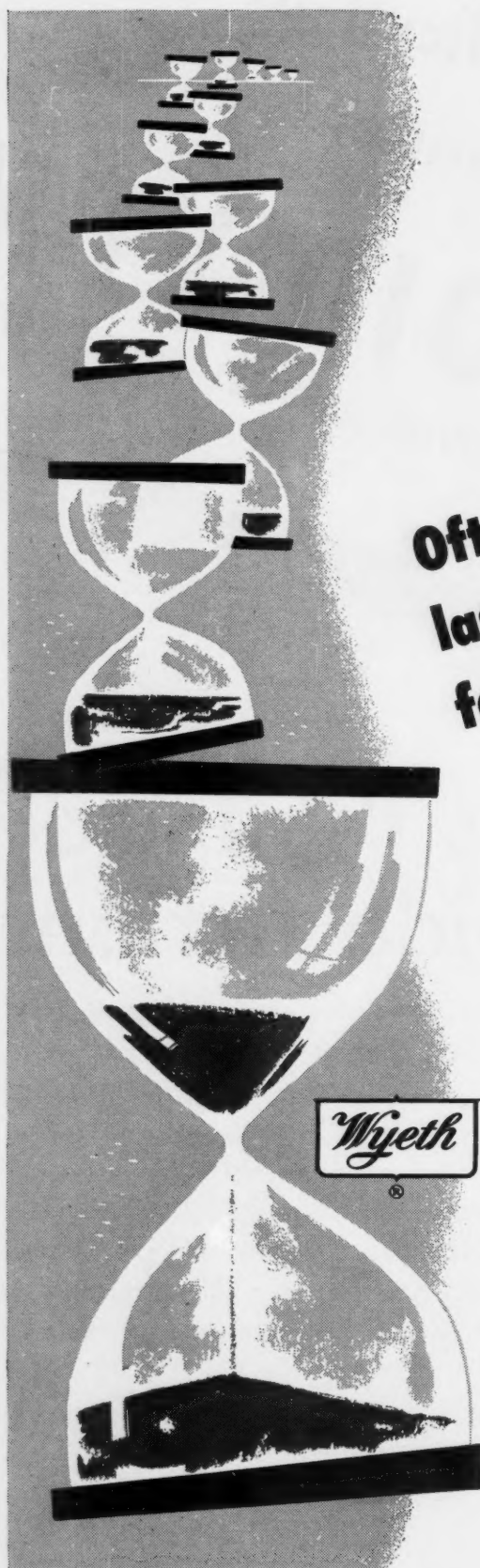
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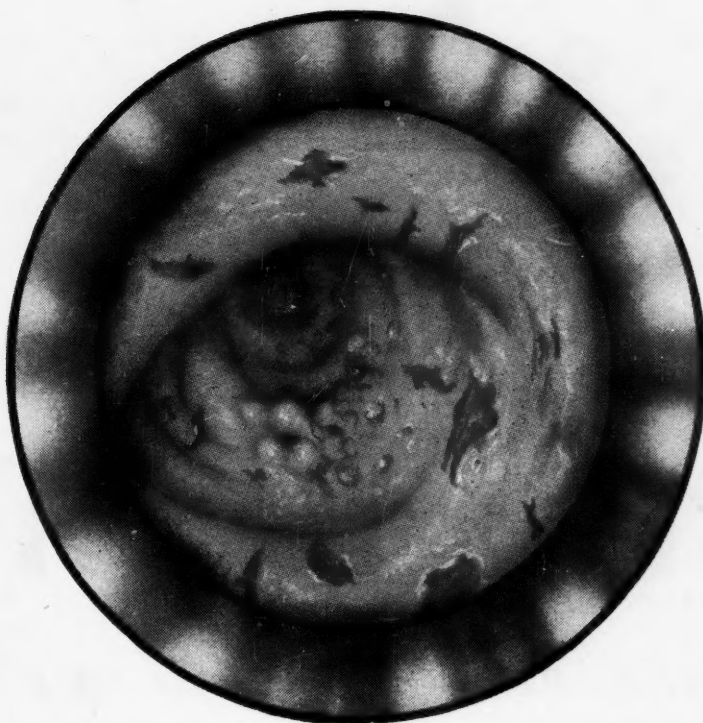
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1. Bain, W. A., Broadbent, J. L., and Warin, R. P.: *Lancet* 2:47, 1949.

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1. Dowling, H. F., et al.: *Ann. New York Acad. Sc.* 53:433 (Sept. 15) 1950.

2. Sayer, R. J., et al.: *Am. J. M. Sc.* 221:256 (March) 1951.

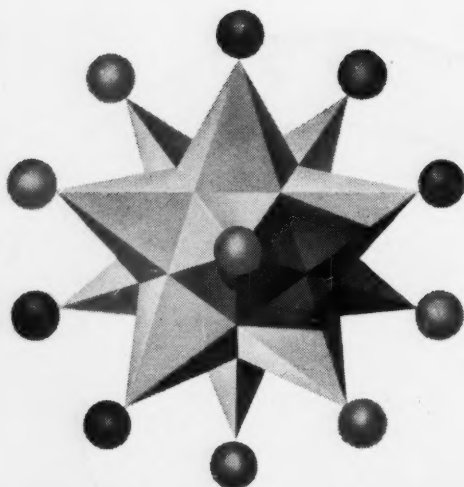
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The American Journal of Medicine

VOL. XI

JULY, 1951

No. 1

Editorial

The First Five Years

FOR the faithful readers of The American Journal of Medicine the current issue has a special significance which should not pass without notice—it is just five years since the appearance of the first number in July, 1946. This, therefore, is an opportune time to weigh the experiences of the past and to consider the place that The American Journal of Medicine has come to occupy in the field of medical publications.

It was with some anxiety that the new venture was launched in 1946. The times were troubled; there seemed already to be a plethora of medical journals; the new publication did not have the moral and financial support of a medical society of large membership; the editor was inexperienced and academically oriented.

The chief impetus behind the founding of the Journal was an idea, really an ideal, which was new and untested. The idea itself was simple and obvious enough. It was to help fill more effectively the gap between the teachings of the great medical schools, hospitals and research institutions of the country and the application of these teachings in practice. As expressed in an introductory editorial outlining the objectives of the new journal, "a principle objective of the American Journal of Medicine is to participate in the currently expanded program for advanced medical education at the postgraduate level. It is not necessary to dilate here upon the long-felt need for integrated postgraduate instruction, more acute now than ever before because of the increasing tempo of advance in both diagnostic and therapeutic methods. To be sure, the most effective teaching is that obtained by personal participation in the activities of highly organized medical schools and teaching hospitals and clinics. Such instruction is available to relatively few, however, and then

usually only for short periods. The teaching opportunities of the medical periodical are therefore very great even though, it must be admitted, often inadequately realized."

To accomplish this objective The American Journal of Medicine has published and will continue to publish conferences and clinics taken directly from the classrooms of institutions in the forefront of medical progress, all painstakingly planned and edited to make effective teaching exercises of sustained interest. A number of outstanding contributions of this kind appear regularly—the Columbia Combined Staff Clinics, the Cornell Conferences on Therapy, the Harvard Conferences on Psychosomatic Problems and the Washington University Clinico-pathologic Conferences. There is abundant testimony to the profound impress these exercises have already made, both in content and in pedagogical method, upon medical education in this country and abroad.

Another major purpose of the new journal was to add to the available media for publication of the results of sound clinical investigation, since it was anticipated that the enlarged programs for medical research made possible by expanding public and private support would require increased publication facilities to make the results rapidly and generally available to practitioners and investigators. Here we have sought a happy medium between highly specialized research of immediate interest to few and repetitious accounts of clinical experiences already familiar to most. Perusal of the pages of the Journal over the past five years will disclose a high proportion of significant additions to medical knowledge, both in the form of detailed presentation of experience and as abstracts of the scientific proceedings of research societies representing various sections of the country.

The steady influx of suitable studies assures continued fulfillment of this important function of *The American Journal of Medicine* which, in this respect also, has acquired a more or less distinctive character as a happy fusion of the clinical and basic sciences. This, again, is in the best tradition of American medicine.

It has become the regular practice of *The American Journal of Medicine* to supplement the two extremes of frank pedagogy and pure experiment with intermediate integrative exercises in the form of symposia, seminars, reviews and editorials. The symposia, which appear in the May and November issues each year, are designed by an authority in the field who serves as guest editor. They deal for the most part with disciplines which should not be but often are separated from the narrow channels of internal medicine, to the disadvantage both of the internist and the specialty discipline. The subjects successively treated thus far include streptomycin, allergy, aviation medicine, syphilis, poliomyelitis, diabetes, viral hepatitis, tuberculosis and the adrenal gland. Many of these symposia have proved to be of such excellence that they have already achieved the stature of standard sources of reference for practitioner and student alike.

The seminars are invited papers generally presenting different points of view on large and usually controversial issues of current interest. These articles appear in sequel form in six consecutive issues of the *Journal*, one broad topic being covered every six months. The subjects covered in this way thus far include rheumatic fever, thromboembolism, hypertension, protein hydrolysates, congestive failure, antibiotics, cancer research, renal physiology and pulmonary physiology. Some of these seminars have attracted such widespread interest that the publishers of *The American Journal of Medicine* have made them available, at cost, in the form of collected bound reprints; and the demand for these has invariably exceeded the supply.

In the selection of review articles preference has been accorded those that give evidence of original investigation and of assimilation rather than mere citation of older work, thus presenting critically integrated and constructive points of view. Opportunity has been afforded also for reasoned speculation, for which a suitable outlet

is so much needed. A number of notable reviews have already appeared, some indubitably sound, others deliberately provocative.

The editorials have, in general, come from the practiced pens of the Editorial Board, all seasoned veterans in teaching and investigation. These editorials have, for the most part, dealt in broad philosophic vein with personal investigative interests or with more general topics of current importance.

In such manner have the Editorial Board and the publishers of *The American Journal of Medicine* endeavored to fulfill the promise of this new venture. Backed by the confidence and support of a growing host of friends, these efforts have translated the *Journal* from a position of hazardous experiment in the projection of advanced clinical research and teaching to an assured place of respect and affection among the established medical journals of the country. For some time now *The American Journal of Medicine* has enjoyed a large, attentive and (as the Editor can attest) discriminating audience. The subscription list has grown steadily and now ranks with the largest in the field of "independent" medical journals (i.e., those not serving as organs of medical societies) appearing monthly.

Such rapid growth and acceptance implies not only that a real need is being met but also defines that need; and therein lies a moral. The *American Journal of Medicine* has made no compromise in the high standards of its material, aiming consistently at those who are interested not only in the immediate application of information but also in the more fundamental and philosophic aspects of disease mechanisms. Surely the success of a *Journal* dedicated to such policy is a reassuring indication of the healthy state of American medicine.

The Editorial Board wishes to take this opportunity to express again its indebtedness to the many who have contributed so generously of their time and energy to increase the effectiveness of the *Journal* in its various programs. The support already received strengthens our resolve to maintain the high standards of the *Journal* and to set our forward course with confidence and determination.

THE EDITOR

Clinical Studies

A New Method of Equating and Presenting Bipolar and Unipolar Extremity Leads of the Electrocardiogram*

Advantages Gained in Visualization of Their Common Relationship to the Electric Field of the Heart

LIEUT. JOHN S. GRAETTINGER, M.C., U.S.N., LIEUT. JOHN M. PACKARD, M.C., U.S.N.
and CAPT. ASHTON GRAYBIEL, M.C., U.S.N.

Pensacola, Florida

THE observations of several investigators have shown that the differences between the bipolar and unipolar extremity leads are not of a fundamental nature but consist of differences in the lead axes and amplitudes of the deflections. Wilson¹ pointed out that the axes of the unipolar leads could be represented as the medians of Einthoven's equilateral triangle. Cohen and Glicksman² demonstrated that tracings quite similar in configuration to the unipolar leads could be obtained by the use of bipolar leads appropriately recorded. Hill³ emphasized that a cardiac vector derived from measurement of the complexes in the unipolar leads was smaller by a factor of $\sqrt{3}$ than a cardiac vector derived from the bipolar extremity leads. Grant^{4,5} has illustrated the application of vector methods to the interpretation of the electrocardiogram using bipolar and unipolar leads.

These observations suggested that a considerable simplification of electrocardiographic interpretation could be effected by certain modifications in the recording and arrangement of the limb leads. By altering the sensitivity of the amplifier the amplitude and area of the deflections in both the bipolar and unipolar leads were made proportional to the projection of the conventional cardiac vector on their axes. By reversal of the polarity of the connections between the electrodes and the amplifier it was possible

to record tracings of reciprocal form representing the changes in the electric field of the heart at diametrically opposite points. When tracings recorded in this manner were appropriately arranged, the common relation of all extremity leads to the electric field of the heart became immediately apparent on inspection of the electrocardiogram.

Observation of electrocardiograms arranged in this manner not only made the relationship between the bipolar and unipolar extremity leads clear but also made apparent that the bipolar and unipolar extremity leads are complementary in that the changes in the mean electric field of the heart are more readily visualized when both are recorded.

Furthermore the application of vector methods to the interpretation of the electrocardiogram was facilitated by these modifications. It was possible to estimate the magnitude and direction of the mean vectors of P, QRS and T in the frontal plane and to draw loops showing the approximate changes in direction and magnitude of the excitation wave during the depolarization process from simple inspection of these electrocardiograms.

It is our purpose in this report to present certain new procedures, to show their validity, to demonstrate how they embrace a number of facts hitherto imperfectly explained and to

* From the U. S. Naval School of Aviation Medicine, Naval Air Station, Pensacola, Fla. Opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the view or the endorsement of the Navy Department.

illustrate their usefulness in clinical electrocardiography.

RELATIONSHIP OF THE EXTREMITY LEADS TO THE ELECTRIC FIELD OF THE HEART

The Electric Field of the Heart. The potential difference which exists between the activated

in all cardiac muscle fibers at a given instant, represents the direction and magnitude of the electric field of the heart at that instant and is termed the *instantaneous cardiac vector*. During the spread of the excitation wave through the heart the cardiac vector progressively changes in magnitude and direction. Wilson⁶ agrees with

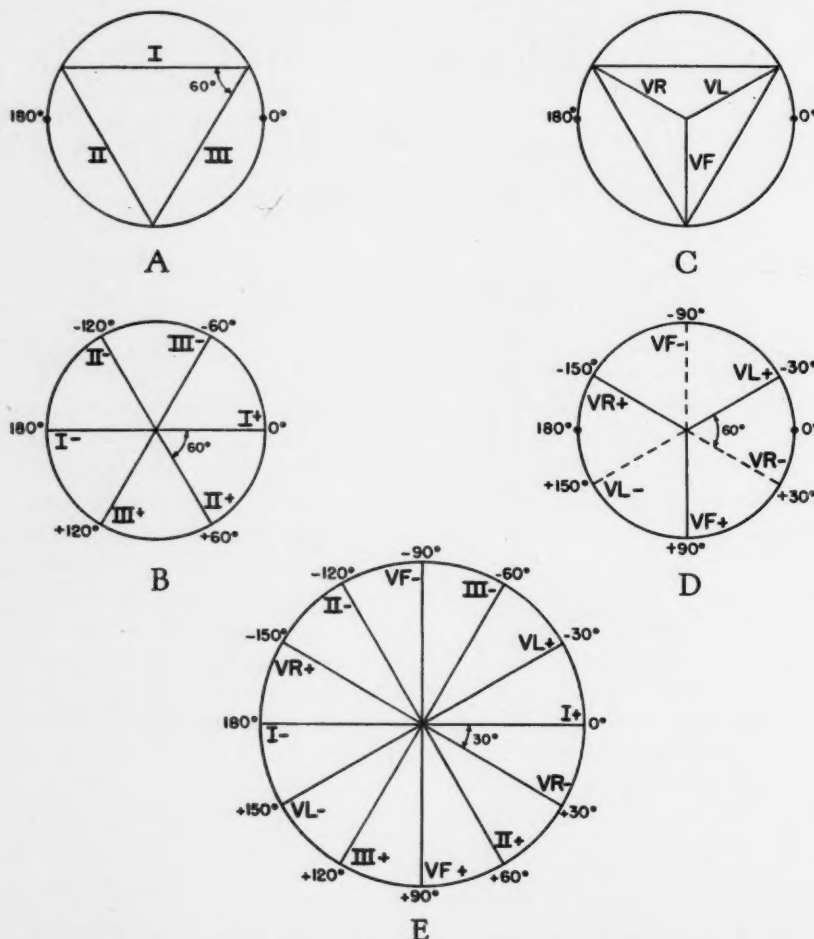


FIG. 1. Development of the hexaxial reference system. A, axes of the bipolar limb leads represented as sides of an equilateral triangle; B, axes of the bipolar limb leads as a triaxial reference system; C, axes of unipolar leads represented as medians of an equilateral triangle; D, axes of the unipolar limb leads as a triaxial reference system; E, hexaxial reference system representing the axes of the bipolar and unipolar extremity leads.

and resting portions of a muscle fiber may be represented as a dipole. The electric field of the dipole may be represented as a vector since it has direction, magnitude and sense. The magnitude of the vector is proportional to the intensity of the current field set up by the dipole, its direction is regarded as parallel to the axis of the dipole and the head of the vector, directed from active toward inactive muscle fiber, is regarded as positive. The resultant of all of the current fields, represented as vectors, existing

Lewis⁷ that the direction of the instantaneous vector corresponds quite closely to the direction in which the excitation wave is spreading through the heart. The direction and magnitudes of instantaneous and mean cardiac vectors may be altered by disease and, as Burgher⁸ has recently pointed out, the relation of heart disease to these vectors can be determined only by medical experience. The relation of cardiac vectors to the electrocardiographic leads, however, is of a purely physical

nature; the complexes seen in the extremity leads are proportional to the frontal plane projection of spatial cardiac vectors on the axes of these leads at successive moments during the cardiac cycle.

constructed by drawing three lines through the center of the triangle which are parallel to the three sides. The resulting figure is enclosed in a circle which is marked off in degrees in a clockwise fashion, according to the electrocardio-

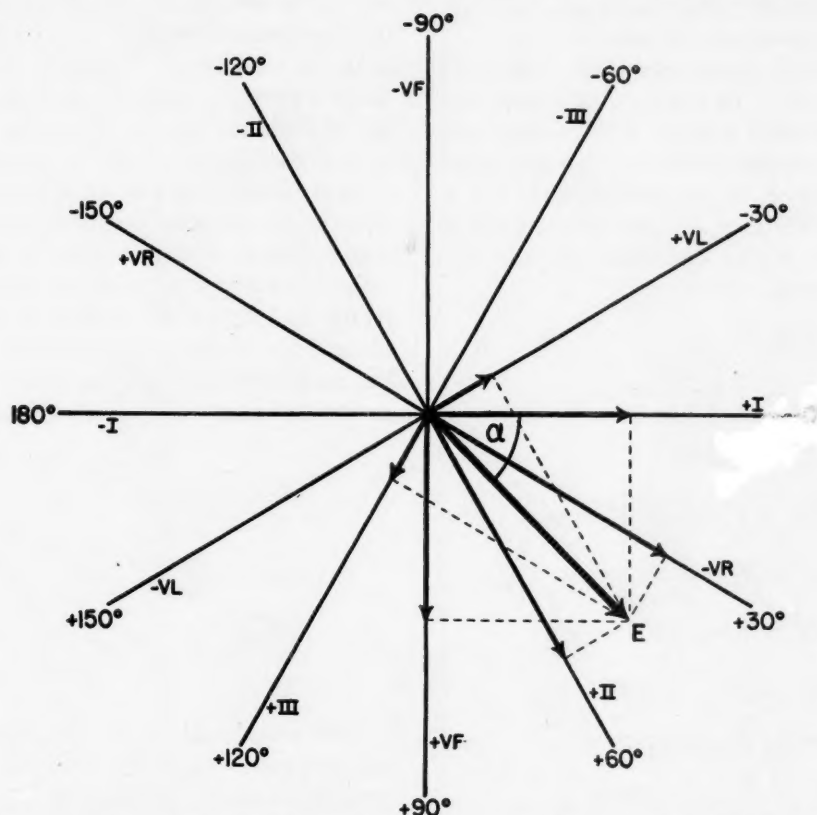


FIG. 2. The projections of a cardiac vector (E) on the axes of the limb leads.

Axes of the Extremity Leads. Einthoven⁹ represented the axes of the bipolar limb leads as the sides of an equilateral triangle. He made certain assumptions, essential to this representation, which are known collectively as the Einthoven hypothesis, namely, that the heart as a source of electric current may be regarded as a dipole in a homogenous conducting medium, equidistant from and in the plane of three points representing the right and left shoulders and the pubis. The limbs are regarded as extensions of the lead wires. Einthoven's hypothesis is essentially in accord with experimental data.¹⁰⁻¹²

Diagrams of the relation of the axes of the bipolar and unipolar extremity leads are shown in Figure 1. The conventional Einthoven triangle is shown in Figure 1A. Of considerably more usefulness in the determination of frontal plane vectors, however, is the triaxial reference system suggested by Bayley in 1944,¹³ a modification of which is drawn in Figure 1B. It is

graphic convention, with the positive end of the axis of lead 1 being marked 0°. This figure may be used in precisely the same manner as the triangle to determine the electric axis of QRS or any other frontal plane vector.

The axes of the unipolar leads may be represented as the medians of the equilateral triangle.¹ They are shown as such in Figure 1c and as a triaxial reference system in Figure 1d. It will be noted that the axes are 60° apart, as are those of the bipolar limb leads, and that the triaxial system representing the unipolar leads is rotated 30° from that representing the axes of the bipolar leads. Finally, the two triaxial systems (Figs. 1b and 1d) may be superimposed (Fig. 1e) to form the useful hexaxial reference system suggested by Pallares.³⁰ Angles between the axes of the extremity leads are the same in the hexaxial reference system as in the Einthoven triangle. The proportionality of the lengths of the axes of the bipolar leads to the

axes of the unipolar leads in the triangle, however, is $\sqrt{3}:1$ (side to median of an equilateral triangle) but in the hexaxial reference system the axes are drawn of equal length. Thus different scales must be drawn on the axes of the bipolar and unipolar extremity leads, as will be discussed in subsequent sections.

Relations between the Amplitudes of the Deflections in the Extremity Leads. In Figure 2 is shown the projection of a cardiac vector (E)* on the axis of each of the extremity leads. In the following equations the relation of the projection (v) of a cardiac vector on the axes of the extremity leads to the magnitude of the deflections in the extremity leads^{9,11} is shown.

VECTOR PROJECTION

$$(1a) \ vVL = E \cos (30^\circ + \alpha)$$

$$(1b) \ vLI = E \cos \alpha$$

$$(1c) \ vVR = E \cos (210^\circ - \alpha)$$

$$(1d) \ vL2 = E \cos (60^\circ - \alpha)$$

$$(1e) \ vVF = E \cos (90^\circ - \alpha)$$

$$(1f) \ vL3 = E \cos (120^\circ - \alpha)$$

MAGNITUDE OF DEFLECTION

$$(2a) \ VL = \frac{E}{\sqrt{3}} \cos (30^\circ + \alpha)$$

$$(2b) \ LI = E \cos \alpha$$

$$(2c) \ VR = \frac{E}{\sqrt{3}} \cos (210^\circ - \alpha)$$

$$(2d) \ L2 = E \cos (60^\circ - \alpha)$$

$$(2e) \ VF = \frac{E}{\sqrt{3}} \cos (90^\circ - \alpha)$$

$$(2f) \ L3 = E \cos (120^\circ - \alpha)$$

From a comparison of the magnitude of the deflection and the vector projection it is seen that:

$$(3a) \ LI = vLI$$

$$L2 = vL2$$

$$L3 = vL3$$

$$(3b) \ VL = \frac{vVL}{\sqrt{3}} = .58vVL$$

$$VR = \frac{vVR}{\sqrt{3}} = .58vVR$$

$$VF = \frac{vVF}{\sqrt{3}} = .58vVF$$

Thus the amplitude of the deflection recorded in a bipolar limb lead is equal to the projection

* The letter E may represent any frontal plane vector, e.g., any instantaneous vector or the mean frontal P, QRS or T vectors. The angle α , the direction of the vector with respect to the axis of lead I, is the "electric axis" of the vector under consideration.

of the conventional cardiac vector on the axis of the lead, but the amplitude of the deflection recorded in a unipolar lead is only 58 per cent of the projection of the conventional cardiac vector on the axis of the lead. A detailed discussion of the reasons for this difference has recently been presented by Hill⁸ and by Burch.¹⁵

If the Goldberger¹⁶ technic of recording unipolar extremity leads is used, the amplitude of the deflections in the unipolar leads is theoretically augmented by a factor of 3/2. The equations relating the amplitude of the deflections in the unipolar leads to the projection of a conventional cardiac vector on the axes of the unipolar leads (3b) may be multiplied by this factor to obtain the theoretic relation of the deflections in the augmented unipolar leads to the projection of a cardiac vector on their axes, as shown in the following equations:

$$(4a) \ aVL = \frac{vVL\sqrt{3}}{2} = .87vVL$$

$$(4b) \ aVR = \frac{vVR\sqrt{3}}{2} = .87vVR$$

$$(4c) \ aVF = \frac{vVF\sqrt{3}}{2} = .87vVF$$

The amplitude of the deflection in an augmented unipolar lead is thus 87 per cent of the projection of a conventional cardiac vector on the axis of the lead.

With respect to the magnitude of a cardiac vector, the unit of amplitude or area (in millivolts or microvolt seconds) in the Wilson unipolar leads recorded at standard sensitivity is therefore equivalent to only 56 per cent of an equal deflection or area as measured in the standard limb leads, and the unit of amplitude or area in the augmented unipolar leads is equivalent to only 87 per cent of an equal deflection or area in the standard limb leads. Thus neither amplitudes nor areas measured in the unipolar or augmented unipolar leads can be

expressed in units of millivolts or microvolt seconds which are equivalent to those used in expressing the magnitude of a cardiac vector as derived from the bipolar leads.

Modifications in Electrocardiographic Technic Which Clarify the Relation of the Extremity Leads to the

Electric Field of the Heart in the Frontal Plane. From the preceding considerations it was apparent that two modifications of electrocardiographic technic could be made which would facilitate the derivation of maximum informa-

of the areas of the complexes in the bipolar leads is greater than that derived from the unipolar leads by a factor of $\sqrt{3}$.

Second, the units of amplitude and area in the unipolar and bipolar leads with respect to

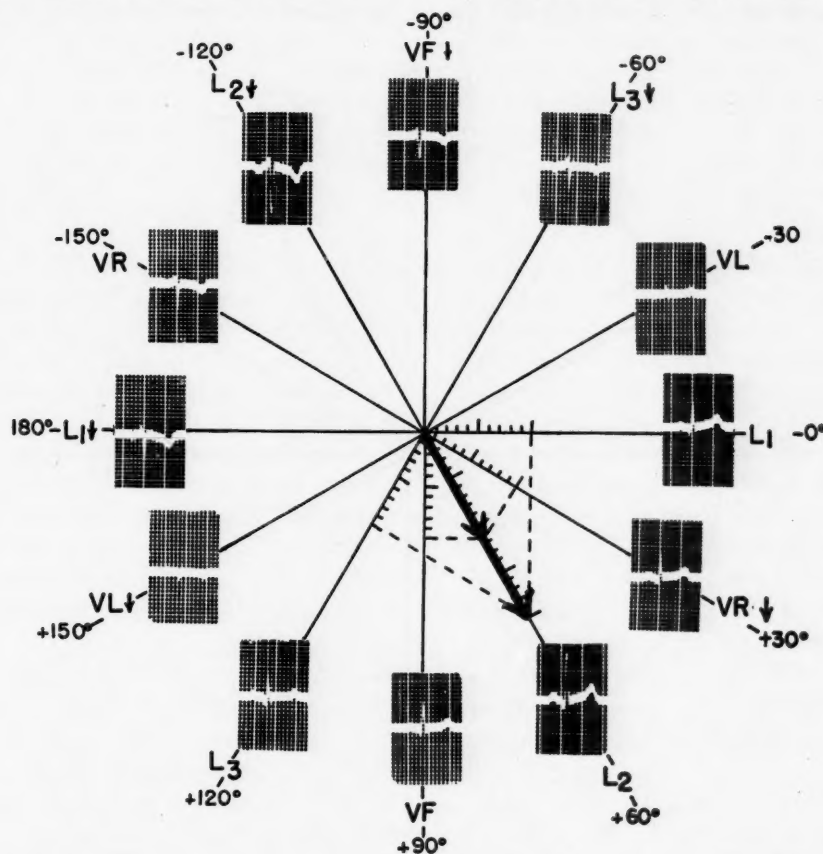


FIG. 3. Bipolar and unipolar extremity leads recorded with conventional and with reversed polarity and mounted at the ends of the axes of the hexaxial system. The scale on all of the axes is identical. \hat{A}_{QRS} is derived from the unipolar leads (11.6 micro-volt seconds) and from the bipolar leads (20 micro-volt seconds).

tion concerning the orientation of the electric field of the heart from the extremity leads.

First, instead of mounting the unipolar and bipolar extremity leads separately they could be mounted at the ends of appropriate axes of the hexaxial system. In order to visualize most readily the inter-relationship of all extremity leads, leads recorded with conventional and with reversed polarity could be mounted in this manner as shown in Figure 3.

In this figure a step-like sequence of form of the deflections is seen in adjacent leads, but the discrepancy between the relative amplitudes of the deflections is marked. The manifest mean axis of QRS (\hat{A}_{QRS}) derived from measurement

"* \hat{A}_{QRS} = manifest mean axis of QRS,—the letter A indicates that the quantities are determined by the areas under the curves of the electrocardiographic deflections, and the arrowhead that the quantities are vectors."¹⁸

the projections of a cardiac vector could be equated either by decreasing the sensitivity of the amplifier when recording the bipolar leads or increasing the sensitivity when recording the unipolar leads.* Since the limits of normal of

* In the study of electrocardiograms recorded at standard sensitivity the magnitude and direction of the conventional cardiac vector may be determined from either the bipolar or the unipolar leads if the scales on the axes of the unipolar leads are appropriately drawn. In Figure 4 is shown a hexaxial system in which the scale on the axes of the unipolar leads is greater than that on the axes of the bipolar leads by a factor of $2/3\sqrt{3}$ or 1.15. The magnitude and direction of \hat{A}_{QRS} , \hat{A}_T , \hat{G} or other cardiac vectors may be determined from electrocardiograms in which the augmented unipolar leads have been recorded by plotting the amplitude or area of the deflections in any two leads, bipolar or unipolar, on appropriate axes of the hexaxial system of Figure 4. The magnitude of a vector derived using this reference system must be read by comparing its length to the scale

the amplitudes and areas of deflections, of the ventricular gradient and of the vectorcardiogram have been determined from the bipolar leads and are expressed in the units derived from mensuration of the bipolar leads, it was preferable to increase the sensitivity of the

from either the deflections in the bipolar or the unipolar leads was the same.

We have designated the unipolar leads recorded in this manner as *vVR*, *vVL* and *vVF*, the prefix "v" (vector) indicating that the amplitude of the deflections is proportional to

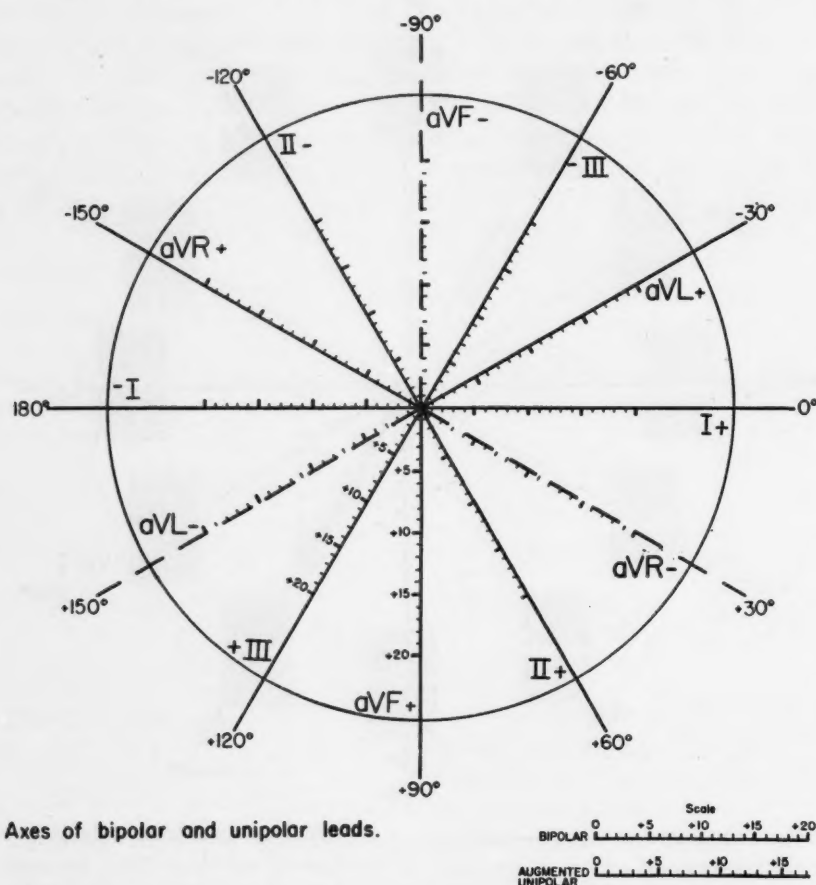


FIG. 4. The hexaxial reference system with the unit of the scale on the axes of the unipolar leads larger by a factor of 1.15 than the scale on the axes of the bipolar leads.

recorder when obtaining the unipolar leads. The sensitivity of the electrocardiograph was therefore increased by a factor of $\sqrt{3}$ when the unipolar leads were recorded, i.e., the unipolar leads were recorded with a sensitivity of 1 mv. = 17.3 mm. (Fig. 5.) The amplitude of the deflections in the unipolar and bipolar leads was now proportional to the projection of the conventional cardiac vector on the axes of these leads, and the magnitude of \hat{A}_{QRS} determined

on the axis of a bipolar lead. A similar hexaxial system may be constructed for use with the bipolar and Wilson unipolar leads if the scale on the axes of the unipolar leads is made greater by a factor of $\sqrt{3}$ than the scale on the axes of the bipolar leads.

the projection of a cardiac vector on the axis of the unipolar lead; this will differentiate these leads from VR, VL and VF and aVR, aVL and aVF.* These leads may also be approximated by setting the sensitivity of the electrocardiograph at 1 mv. = 11.5 mm. ($2/3\sqrt{3}$) when using the Goldberger¹⁶ method of augmenting unipolar leads.

In the electrocardiogram shown in Figure 5 not only is the step-like sequence in form of the deflections apparent but also the sequence in amplitude of the deflections in adjacent leads. The P wave is essentially isoelectric in *vVL*,

* When the vector unipolar leads are used, the equations relating the amplitudes of the deflections obtained

slightly positive in lead I, more positive in $vVR\downarrow$ most positive in lead II, less positive in vVF and only slightly positive in lead III. A small Q appears first in lead I, reaches its maximum amplitude in lead II and then progressively diminishes. A small R appears in vVL , increases in leads I and $\downarrow vVR$, is maximum in lead II and becomes smaller in leads vVF and III. The serial differences in amplitude of the T wave are obvious. The same sequence of deflections is, of course, seen in the leads recorded with reversed polarity with a reversal of sign of the deflection.

In Figure 5 it will be noted that the sum of the positive and negative areas of the QRS deflections is essentially zero in two leads, vVL (axis at -30°) and $vVL\downarrow$ (axis at $+150^\circ$). A line connecting -30° with $+150^\circ$ divides the circle of the hexaxial reference system into two hemicircles, one of which faces the leads in which the mean QRS deflections are positive and the other the leads in which the mean QRS deflections are negative. The 180° arc of the positive hemicycle begins and ends at the points which mark the transition of the mean QRS deflections from negative to positive (-30°) and from positive to negative ($+150^\circ$), respectively, and crosses all of the axes of the leads in which the mean QRS is positive. The vector \hat{A}_{QRS} , which represents the mean direction of the QRS forces, is at right angles to the diameter of this hemicycle. It can thus be seen that this 180° of arc crosses all of the axes of the leads on which a projection of this vector can be drawn, and begins and ends at the axes on which no projection can be drawn.

in the various limb leads must be revised as follows from equations (1 and 2):

$$vVL - vVR = E \cos (30^\circ + \alpha) - E \cos (210^\circ - \alpha) \\ = (E \cos \alpha) (\sqrt{3}) = L1 \sqrt{3}$$

$$\text{thus: } L1 = \frac{vVL - vVR}{\sqrt{3}}$$

$$\text{similarly, } L2 = \frac{vVF - vVR}{\sqrt{3}}$$

$$L3 = \frac{vVF - vVL}{\sqrt{3}}$$

$$\text{and } vVR = - \frac{L1 + L2}{\sqrt{3}}$$

$$vVL = \frac{L1 - L3}{\sqrt{3}}$$

$$vVF = \frac{L2 + L3}{\sqrt{3}}$$

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In each of the three subsequent illustrations the positive arc for the QRS deflections is shown and in addition the positive arc for the T deflections. In each case it will be noted that the arcs cover 180° , that the diameters of the hemicycles connect the transition points of the mean QRS and T deflections respectively, and that the 180° arcs of QRS and T do not represent the same portions of the perimeter of the hexaxial reference system.

It will also be noted that the complexes of maximum area appear at the end of a radius of each hemicycle which is at right angles to the diameter, as was shown in Figure 5 with regard to \hat{A}_{QRS} . This radius, of course, corresponds in direction to that of \hat{A}_{QRS} or \hat{A}_T . It can also be seen that the area of the deflections progressively decreases in the leads facing the 90° of arc on either side of this radius as the transition points are approached. The opposite sequence appears in the leads located on the negative sides of the diameters connecting the transitional points, i.e., those which would face the negative hemicycles which have been omitted from these three figures.

In Figure 6 is shown the electrocardiogram of a healthy young man. The QRS deflections are positive from -65° to $+125^\circ$ in clockwise fashion and the T deflections follow a closely similar pattern.

The electrocardiogram in Figure 7 is that of a patient with hypertensive heart disease and left ventricular hypertrophy. The transition points for QRS and T are both quite close to $+90^\circ$ and -90° , (the axis of vVF), but the QRS complexes are positive in leads whose axes are located from -90° to $+90^\circ$ whereas the T deflections are positive in the leads from $+90^\circ$ to -90° . The marked divergence of the positive QRS and T arcs is apparent.

In Figure 8 is shown an electrocardiogram of a five year old boy with pulmonary atresia, over-riding of the aorta, a large patent ductus arteriosus and marked right ventricular hypertrophy. The marked divergence of the arcs of QRS and T is again seen. The augmented unipolar leads are shown with the bipolar leads in this illustration. Although the amplitude of the deflection in an augmented unipolar lead represents only 87 per cent of the amplitude of an equivalent deflection in a bipolar or vector unipolar lead, the step-like sequence of the deflections in adjacent leads is clear.

It is apparent that the relation of the deflec-

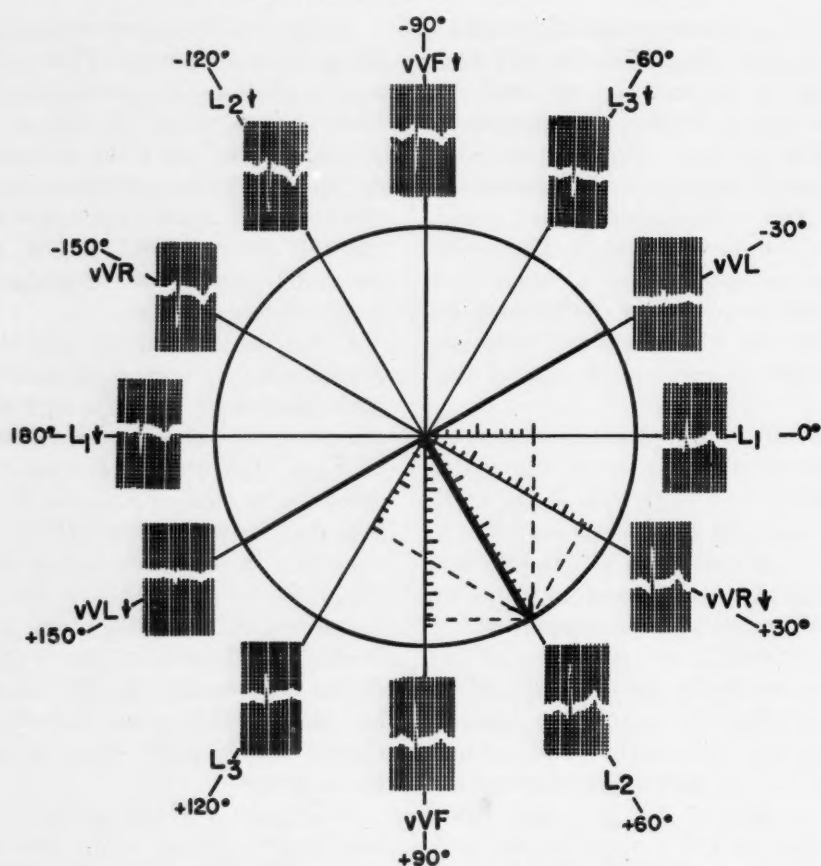


FIG. 5. Electrocardiogram of same subject as in Figure 3 with bipolar leads recorded at standard sensitivity and unipolar leads recorded at a sensitivity of 17.3 mm. = 1 m.v. (= vector unipolar leads). $\hat{A}QRS$ is now 20 micro-volt seconds when derived from any two of the twelve leads.

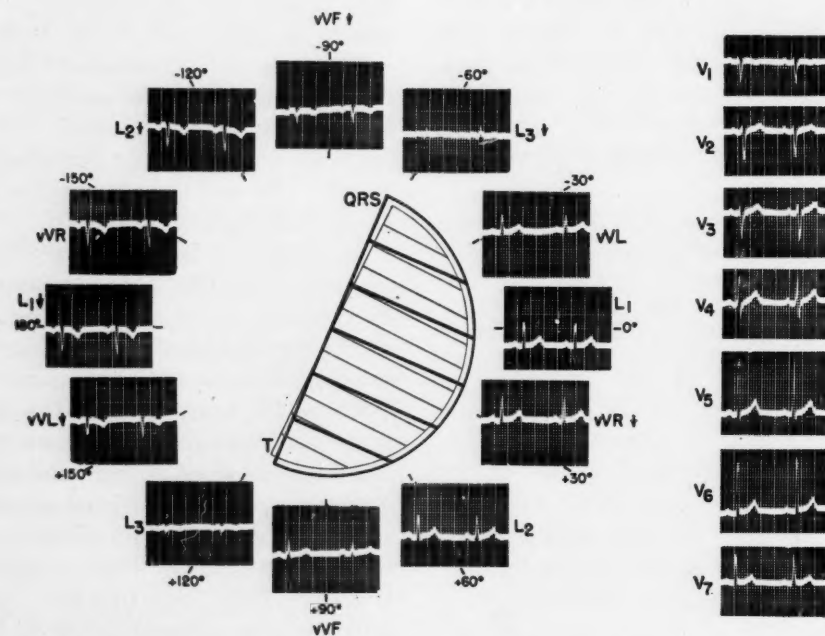


FIG. 6. Bipolar and vector unipolar extremity leads recorded and mounted as in Figure 4 in a normal subject.

tions in all of the extremity leads to each other and to the orientation of the electric field of the heart can readily be appreciated when certain changes in recording and mounting of the extremity leads are made.

projection of the vector is thus on the axis of lead I and no projection can be drawn on the axis of vVF. Therefore the greatest deflection at .01 second appears in lead I and no deflection appears in lead vVF, resulting in an isoelectric

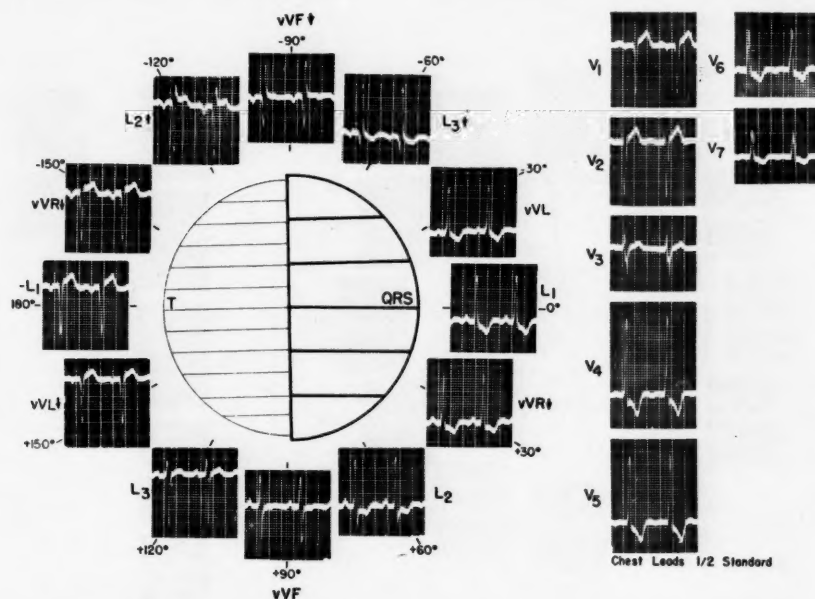


FIG. 7. Bipolar and vector unipolar extremity leads in a patient with marked left ventricular hypertrophy. The positive QRS arc is deviated to the left (counter-clockwise) toward the left ventricle and the positive T arc to the right (clockwise) away from the left ventricle in the frontal plane.

DETERMINATION OF CARDIAC VECTORS

These changes in electrocardiographic technic greatly facilitate the determination of the magnitude and direction of cardiac vectors, as will be shown in this section.

The relation of the amplitude and direction of the deflections in seven frontal plane leads, vVR, vVL, I, reversed vVR (\downarrow vVR), II, vVF, and III during the QRS interval is shown diagrammatically in Figure 9. The positions of the cardiac vector at .01 to .07 second are shown as instantaneous vectors on the hexaxial system. The amplitude of the deflection in any lead is proportional to the projection of the instantaneous vector on the axis of the lead. The sign or direction of the deflection is determined by projection of the vector on the positive or negative portion of the axis of the lead since the signs at the ends of the axes indicate the polarity of the connections of the leads to the positive and negative lead wires from the electrocardiograph machine.

At .01 second the vector is directed along the negative portion of the axis of lead I and makes a right angle with the axis of vVF. The greatest

origin of the QRS complex in this lead. Smaller projections of the vector may be drawn on the axes and thus smaller deflections appear in the leads vVL, vVR, II and III. Since the projection of the vector is on the negative portions of the axes of leads vVL, I and II, the deflection is negative in these leads; the projection of the vector is on the positive axes of leads vVR and III and thus the deflections at .01 second are positive in these leads.

It will be noted that the lead labeled \downarrow vVR is an inverted image of lead vVR. It is derived from the seven instantaneous vectors in the diagram by reversing the signs at the end of the axis of vVR. The positive portion of the axis of \downarrow vVR is thus the negative portion of the axis of vVR. The projection of the .01 vector, for example, is on the negative portion of the axis of \downarrow vVR and thus the deflection at .01 is negative in lead \downarrow vVR and exactly equivalent to the positive deflection in lead vVR.

The instantaneous vector at .02 second is directed along the positive portion of the axis of vVF at right angles to the axis of lead I, thus the deflection at .02 second is maximum in lead

vVF and is positive while no deflection appears at this instant in lead I. The projections of the vector are on the positive portions of the axes of leads \downarrow vVR, II and III and the negative portions of the axes of vVR and vVL; thus the deflections at .02 second are positive in leads II,

the electrocardiogram.⁴ The basis of this method of determining the direction of frontal plane vectors lies in the fact that at a given instant during the cardiac cycle no deflection is seen in a lead the axis of which is at right angles to the direction of the cardiac vector at that instant.

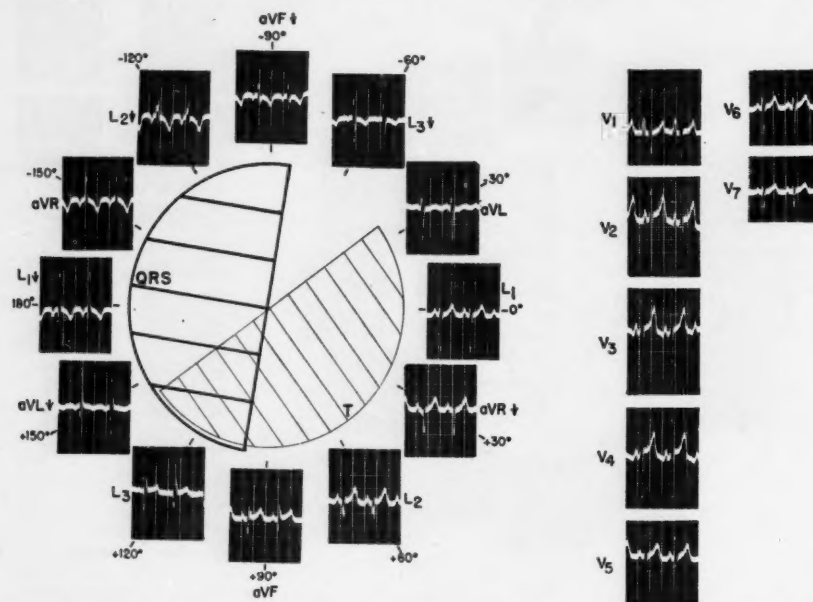


FIG. 8. Bipolar and augmented unipolar extremity leads in a patient with marked right ventricular hypertrophy. The positive QRS arc is deviated toward the right ventricle in the frontal plane and the positive T arc away from the right ventricle.

III and \downarrow vVR as well as in vVF and negative in leads vVR and vVL.

Analysis of the relation of the deflection seen in each of the extremity leads to the instantaneous vectors at .03 to .07 second may be carried out in a similar manner. In the diagrammatic representation in this figure the complexes derived from the projection of the cardiac vector at successive instants on the axes of the unipolar leads are, of course, equivalent in amplitude to the vector unipolar leads. On inspection of the complexes seen in the seven leads, bipolar and vector unipolar, the relation of the configuration and magnitude of the deflections at successive instants to the cardiac vector is clear, e.g., the common genesis of the initial downstrokes in leads vVL, I, \downarrow vVR, II, and the initial upstroke in leads III and vVR; the common production of the final portion of the R wave in leads vVL, I and the S wave in leads II, vVF and III.

When the leads are mounted in this manner, the determination of the direction of the mean frontal P, QRS and T vectors is quite simple and indeed can be accomplished by inspection of

Similarly an isoelectric interval or equal positive and negative areas of the P, QRS or T waves will be seen in the lead the axis of which is at right angles to the direction of the mean frontal P, QRS or T vectors. In Figure 9 no deflection is seen in lead vVF at .01 second after the beginning of the QRS interval and the .01 vector is at right angles to the axis of vVF. No deflection is seen in \downarrow vVR (or in vVR) at .07 second and the vector at .07 second is at right angles to the axis of vVR. The greatest deflection of the QRS complex is the R wave in lead II which reaches its peak at .04 second, and at that instant no deflection is seen in lead vVL, the axis of which is at right angles to that of lead II. Furthermore the sum of the positive and negative areas of the QRS complex in vVL is equal to zero and thus the manifest mean axis of QRS (\hat{A}_{QRS} , "electric axis of QRS") is at right angles to the axis of lead vVL; its direction therefore could be either $+60^\circ$ or -120° . Since the sum of the QRS deflections in lead II is positive, its direction must be $+60^\circ$, i.e., the projection of \hat{A}_{QRS} must be on the positive portion of the axis of lead II.

In the electrocardiogram shown in Figure 5 it was noted that the sum of the areas of the QRS deflections above and below the baseline in lead vVL is equal to zero, i.e., that the complex in lead vVL marks the transitional point from positive to negative for the QRS complex.

tions is positive. The direction of any vector may be determined in this manner. The direction of \hat{A}_P (the axis of P) is obtained in Figure 5, for example, by noting that the P wave is essentially isoelectric in lead vVL, i.e., the transitional point of the P vector is at -30° . The P wave is

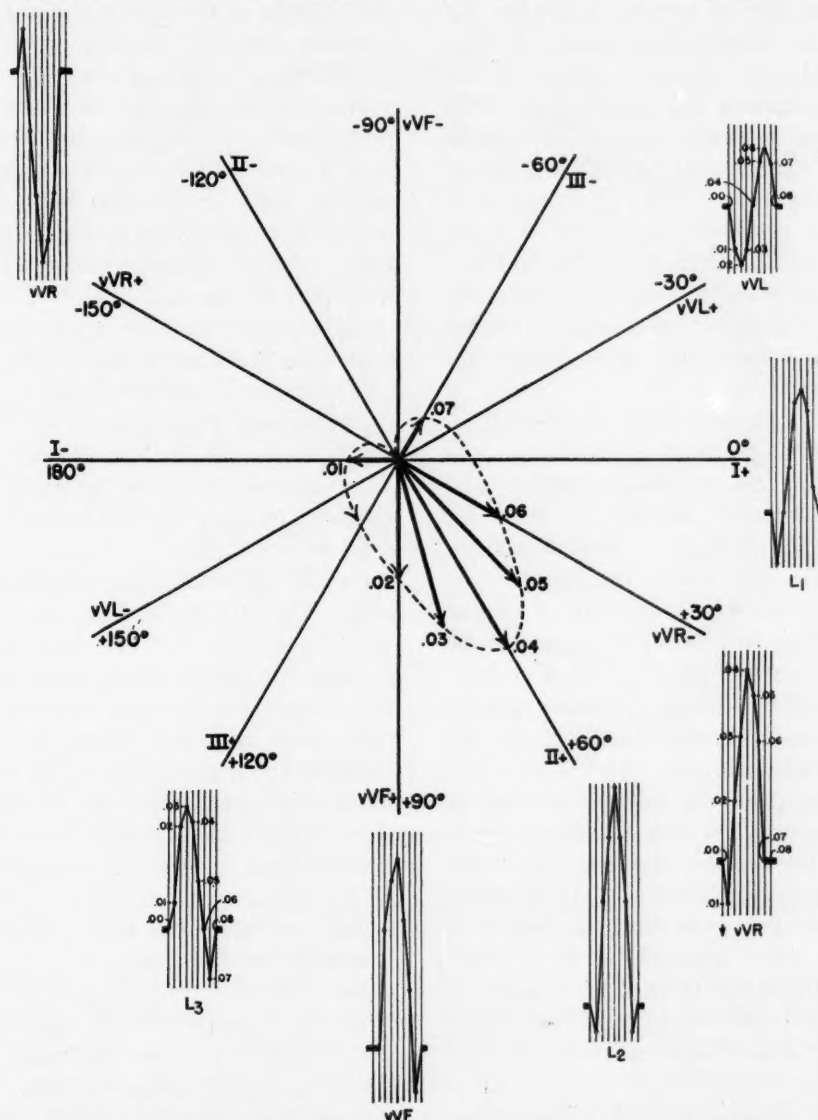


FIG. 9. The relation of the complexes in the extremity leads to the magnitude and direction of the cardiac vector at seven instants during the QRS interval.

Thus the direction of \hat{A}_{QRS} which was laboriously derived in this electrocardiogram from measurement of the areas of the QRS deflections in all of the leads and found to be $+60^\circ$ could quite easily be determined by inspection.

In general, to determine the direction of a frontal plane vector one need only determine the location of a transitional point in degrees from inspection of the electrocardiogram; the vector must be directed 90° away toward the leads in which the sign of the deflec-

upright in lead II, the axis of which makes a right angle with that of vVL, and therefore the direction of the P vector is at $+60^\circ$.

The transitional point of a vector usually does not lie exactly parallel to the axis of one of the extremity leads. Thus in Figure 5 the transitional points for the T vector (\hat{A}_T) are midway between the axes of vVL and L3 \downarrow and the axes of vVL \downarrow and L3 since the positive area of T_{vVL} is equal to the negative area of $T_{L3\downarrow}$ and the negative

area of $T_{vVL\downarrow}$ is equal to the positive area of T_3 ; the transitional points are thus -45° and $+135^\circ$. Since the T wave is positive in leads $\downarrow vVR$ and II, the T vector is at $+45^\circ$ ($+135^\circ - 90^\circ$, or $-45^\circ + 90^\circ$).

When the twelve limb leads are recorded, two transitional points are of course available for each portion of the electrocardiogram. In Figure 5, for example, the diameter dividing the plane circle representing the mean QRS field into positive and negative halves is drawn through the two transitional points of QRS at -30° and $+150^\circ$ and the mean QRS vector is the radius of the positive semicircle at right angles to this diameter. Similarly, in Figures 6, 7 and 8 the mean QRS and T vectors are directed along the radii of the semicircles at right angles to the diameters connecting the transitional points of QRS and T.

When only six extremity leads are available, only one transitional point of a vector can appear. Occasionally no transition point will appear for a particular vector. If only six extremity leads, vVL to lead III, were available in the electrocardiogram shown in Figure 5, for example, no transitional point for the T vector would appear. This will occur for any vector which lies between $+31^\circ$ and $+59^\circ$ or -121° and -149° since the transitional points for such vectors will be more counterclockwise on the hexaxial system than the axis of vVL at -30° or more clockwise than the axis of lead III at $+120^\circ$. The transitional points of such a vector may be readily determined, however, by comparing the relative magnitude of the deflection represented by the vector in leads III and vVL since $L3\downarrow$ is at -60° and $vVL\downarrow$ at $+150^\circ$. Thus if only the usual six leads of the tracing in Figure 5 were available, the equal amplitude of T_3 and T_{vVL} would indicate that T_3 and $T_{vVL\downarrow}$, and $T_3\downarrow$ and T_{vVL} would be of the same area but opposite in sign, i.e., that the transitional points would lie midway between -30° and -60° and $+120^\circ$ and $+150^\circ$.

This technic for determination of the direction (axis) of frontal plane vectors is obviously more simple than those which involve computing the actual magnitude of the deflections in two leads and then deriving the axis from the Einthoven triangle,¹⁷ triaxial or hexaxial systems, Dieuaide chart,¹⁸ the use of tables^{19,20} or slide rule.²¹ It is of more value than Lewis' index method²² since a definite value is obtained. The direction of the vector obtained from the transitional point

method is always that of the mean manifest axis, i.e., that which would be derived from measurement of the areas of the complexes. The electric axis of an electrocardiogram, however, as obtained from measurement only of the amplitude of deflections without consideration of the relative widths of the various waves, often diverges considerably from the direction of \hat{A}_{QRS} because of dissimilar widths of the Q, R and S waves in various leads. Because of the frequent lack of proportionality between the amplitude of the P and T waves in an electrocardiogram and the area of the P or T deflections, the electric axis of P or T, determined by measurement of amplitude, usually is quite different from the actual direction of \hat{A}_P and \hat{A}_T ; but the direction of these vectors may be quite accurately determined by the transitional point technic.

The error introduced when the augmented unipolar and bipolar leads are used is small, as may be shown in the following example: If T_{aVL} appears to be of the same area as T_I but opposite in sign, the transitional point might be read as -15° . Since, however, the area of T_{aVL} is only 87 per cent of the length of the projection of the T vector on its axis, the transitional point would actually be -10° , an error of 5° in determining the transitional point and hence of the direction of the T vector. An error of this magnitude is of no consequence for clinical electrocardiography since one often sees the area in leads near the transitional points of P, QRS or T vary from slightly negative to slightly positive during quiet respiration, a variation of direction of the vector of about 5° .

Since a vector lies most nearly parallel to the axis of the lead in which the maximum deflection occurs, its direction may also be determined from the complexes of maximum amplitude. This method is more difficult than the use of the transitional point technic, however, since the relative amplitudes of the deflections in the leads whose axes are immediately adjacent to that of the lead in which the maximum deflection occurs must be determined and the direction of the vector derived by interpolation. Furthermore, since the augmented unipolar and bipolar leads are usually recorded, a small error is introduced by the disproportionate amplitudes of the deflections in these unipolar and bipolar leads. This latter error does not obtain, of course, when the *vector* unipolar and bipolar leads are available.

The general configuration of the frontal plane

QRS vectorcardiogram may also be determined from electrocardiograms recorded in this manner. In Figure 9 the dotted loop connecting the heads of all of the instantaneous vectors approximates the QRS loop of the vectorcardiogram.* From inspection of the configuration

num deflections at successive instants. Thus the initial portion of the loop toward the negative half of the axis of lead I is small compared with its size at .04 second, as can be seen from the small amplitude of Q_1 compared with R_2 . The remainder of the loop in this diagram may

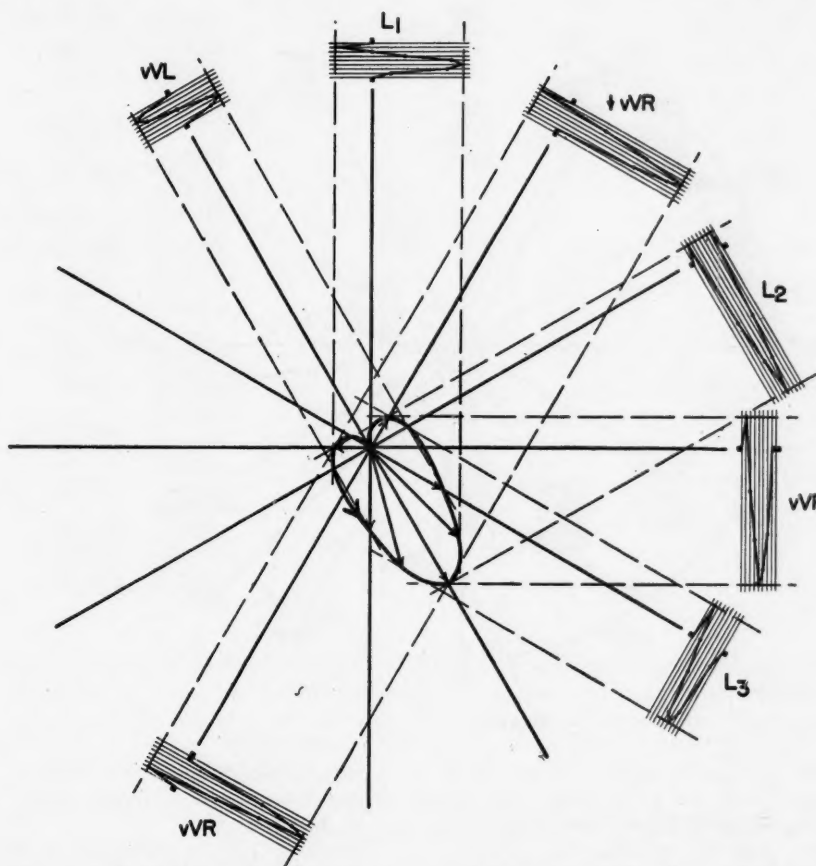


FIG. 10. Method for determining the contour and magnitude of the QRS loop of the vectorcardiogram from the bipolar and vector unipolar leads.

and amplitude of the deflections in the limb leads as derived in this diagram the general shape of the QRS loop may be determined by visualizing the direction and size of the instantaneous QRS vectors. That the first portion of the loop is directed toward the negative axis of lead I is seen by the negative deflection initially in lead I, the transition point in vF and the initial positivity in lead III. The relative size of different portions of the loop may be estimated from the relative amplitudes of the deflections in the leads which show the maxi-

be visualized by noting in similar fashion the direction of the deflection in the leads, their relative magnitudes and transitional points at successive instants during the cardiac cycle.

The vectorcardiogram may be estimated with greater precision by mounting the leads at right angles to their axes and confining the loop within the lines drawn perpendicular to the axes through the points of maximum deflection. An illustration of this method for deriving the frontal plane QRS loop from the extremity leads is shown in Figure 10 in which the complexes obtained in Figure 9 were mounted at right angles to their axes. Following Wilson's²³ and Bayley's²⁴ techniques the leads are mounted so that the resulting loop is in the same quadrant as the mean QRS vector (electric axis) of the normal

* A precise vectorcardiogram is recorded by photographing the three loops (P, QRS and T) formed on a cathode ray tube, suitably connected to the patient, by the movement of the electron beam which marks the terminus of the cardiac vector at each instant during the cycle.

electrocardiogram. Leads $\downarrow vVR$, II, vVF and III must therefore be mounted upside down. The correspondence of the loop in Figure 10 to that of Figure 9 is seen.*

In addition the vector unipolar leads, the hexaxial reference system and the transitional

whose axis is most nearly parallel to the mean QRS vector and this value is plotted on the scale along the axis of that lead. From this point a perpendicular is erected to the line indicating the direction of the mean QRS vector. This intersection marks the terminus of \hat{A}_{QRS} , for the

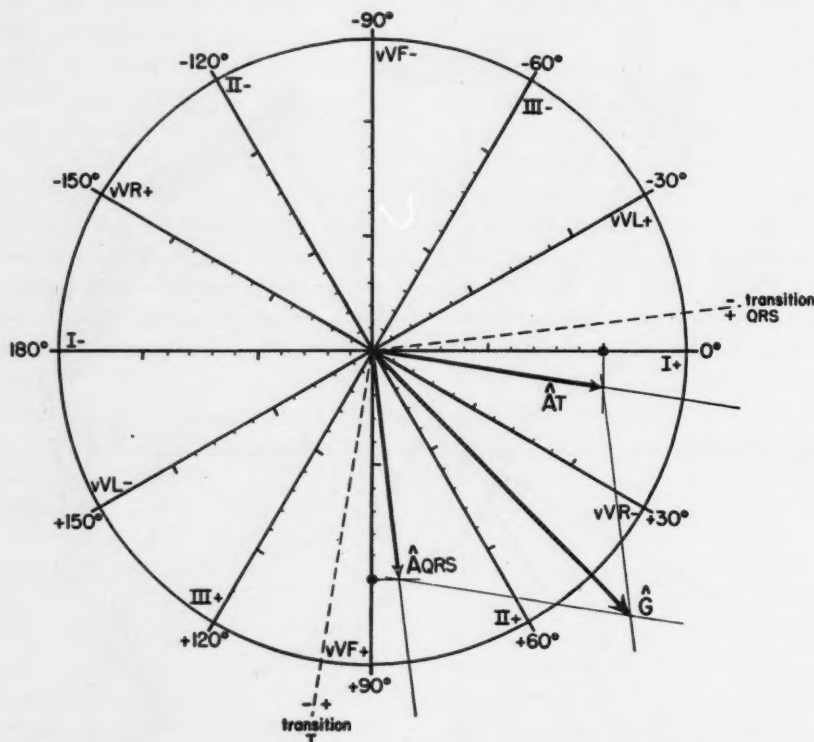


FIG. 11. An illustration of the use of the vector unipolar leads, the hexaxial system and the transitional point technic for determination of the direction and magnitude of \hat{A}_{QRS} , \hat{A}_T and the ventricular gradient (\hat{G}).

point technic provide an easy means of determining not only the direction but also the magnitude of \hat{A}_{QRS} and \hat{A}_T , and of approximating the ventricular gradient (\hat{G}). (Fig. 11.) The direction of the mean QRS vector is determined by location of its transitional point and drawn on the hexaxial system. The net area† of the QRS deflection is then measured in the lead

* The schematic tracings in Figures 9 and 10 were derived from the seven instantaneous vectors. The QRS loops were symmetrically drawn through the termini of these vectors. It will be noted that since the terminal portion of the loop projects on the negative section of the axis of $\downarrow vVR$ and the initial portion on the negative section of the axis of vVF a small $S\downarrow vVR$ and $QvVF$ would appear if the tracings had been derived from these symmetric loops.

† The net area of any deflection may be approximated by regarding it as a triangle, as suggested by Ashman,¹³ and determining the product of one-half of the amplitude in millivolts and the width at the baseline in hundredths of a second. The area thus obtained is expressed in micro-volt seconds.

magnitude as well as the direction of the mean QRS vector have been established. In like manner \hat{A}_T is determined. \hat{A}_{QRS} and \hat{A}_T are then added by construction of a parallelogram as illustrated. The diagonal of this parallelogram, the vector sum of \hat{A}_{QRS} and \hat{A}_T , represents the direction and magnitude of the ventricular gradient in the frontal plane (\hat{G}). The actual magnitude of the ventricular gradient may be obtained by comparing its length with the scale on the axis of any lead.

When the augmented unipolar leads have been recorded with the bipolar leads, the magnitude as well as the direction of cardiac vectors may be easily approximated if a hexaxial system is used in which the unit of the scale on the axes of the unipolar leads is appropriately larger than the unit of the scale on the axes of the bipolar leads (Fig. 4) and the procedure previously outlined is followed. Determination of the gradient by this method is not precise since the

difference in the relative amplitudes of the deflections in the two sets of leads introduces a possible error into the determination of the directions of \hat{A}_{QRS} and \hat{A}_T by inspection. The amplitude of the deflections in the unipolar leads recorded at standard sensitivity (VR, VL

tions only six extremity leads are shown mounted according to the angles their axes make with the axis of lead I, namely, leads aVL, I, \downarrow aVR, II, aVF and III. Since the amplitude of the complexes in the augmented unipolar leads is only 87 per cent of those in the vector unipolar leads,

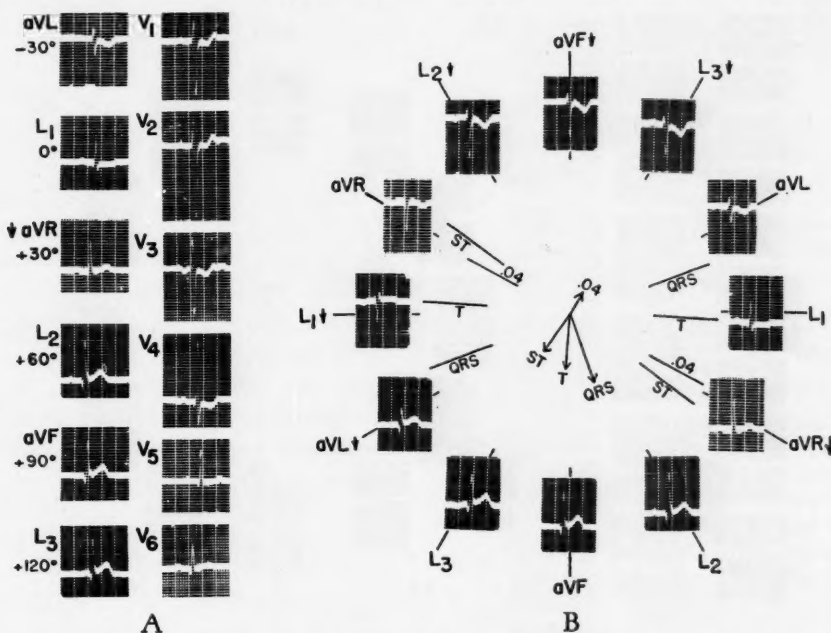


FIG. 12. The orientation of electrical forces in an electrocardiogram from a patient with acute posterior myocardial infarction. A, bipolar and augmented unipolar extremity leads and unipolar precordial leads; B, twelve leads mounted around the hexaxial system with transitional points and directions of 0.04 ("Q"), QRS, ST and T forces indicated.

and VF) is too small compared with that in the bipolar leads to allow application of this technic for the determination of the gradient.

In summary it may be pointed out that when certain modifications are made in the recording and mounting of electrocardiograms the direction of mean or instantaneous cardiac vectors and the general form of the vectorcardiogram may be derived by inspection. Furthermore both the magnitude and direction of \hat{A}_{QRS} , \hat{A}_T and the ventricular gradient may be easily determined by measurement of the area of one QRS and one T deflection and plotting on the hexaxial system.

EXTREMITY LEADS IN CLINICAL ELECTROCARDIOGRAPHY

The application of vector methods to the interpretation of the electrocardiogram⁵ or the interpretation of tracings by any method is considerably simplified when some of the modifications in electrocardiographic technic shown heretofore are made. In the following illustra-

a discrepancy of 13 per cent exists between the relative amplitude of the deflections in the bipolar and those in the augmented unipolar leads. As will be seen, however, this disparity in amplitudes does not interfere with the determination of the *orientation* of the electric field by inspection.

The electrocardiograms in Figure 12 are those of a twenty-two year old man with complaints of severe substernal pain, dyspnea, weakness and nausea who was seen for the first time on the day the electrocardiogram in Figure 12A was recorded. A minor bout of similar pain had occurred four days prior to examination. The Q wave of .04 duration in lead III, accompanied with elevation of the S-T segment in leads II, aVF and lead III, with reciprocal depression in leads aVL, I and the leads from the right precordial region, are consistent with acute ischemia and infarction of the "posterior" wall of the left ventricle. A small Q wave appears in lead I of approximately .02 second duration and becomes progressively wider until it is of .04 second

duration in lead III. The R is small in $\downarrow aVL$, increases in leads I and $\downarrow aVR$, is maximum in amplitude in lead II and of less magnitude in aVF and III. There is a deep S in aVL , considerably less in lead I and the last .02 second of the QRS interval is almost isoelectric in $\downarrow aVR$.

Since the S-T segment is isoelectric in lead $\downarrow aVR$, negative in leads located counterclockwise to the axis of $\downarrow aVR$ and positive in lead-located clockwise to the axis of $\downarrow aVR$, an ST vector may be drawn at right angles to the axis of this lead, parallel to the axis of lead III. The

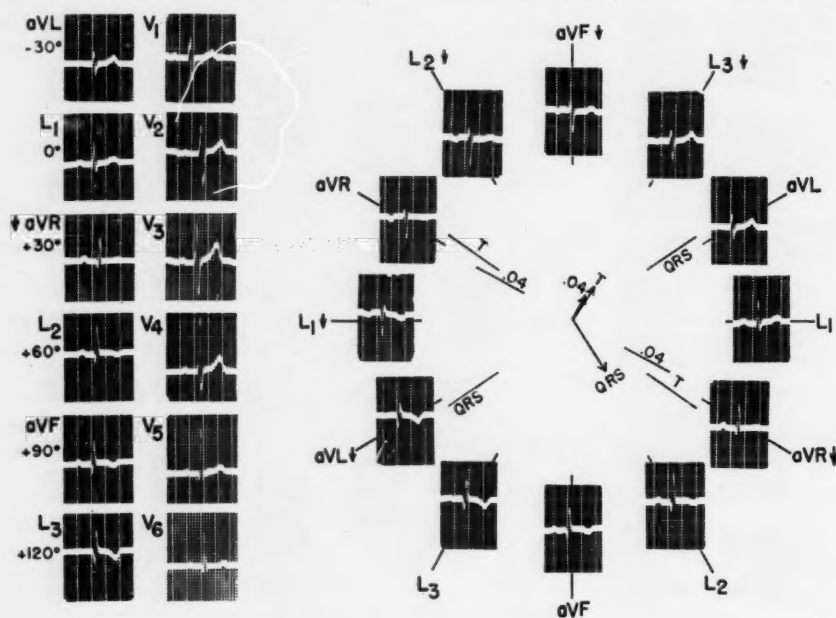


FIG. 13. An electrocardiogram recorded six weeks after the tracing in Figure 12 in the same patient.

In leads II, aVF and III the terminal portion of the R waves becomes more slurred. The S-T segment is depressed in aVL , somewhat depressed in lead I, isoelectric in $\downarrow aVR$ and progressively more elevated in leads II, aVF and III. The T is inverted in aVL , very slightly inverted in lead I and of progressively greater amplitude in the remainder of the extremity leads. In Figure 12b the leads are mounted around the hexaxial system with the transitional points for the various vectors drawn within the circle formed by the leads. The vectors are drawn at right angles to the lines indicating the transitional points.* The transitional point for QRS lies slightly to the right of the axis of aVL (-30°) as the complex in this lead is very slightly negative and is strongly positive in lead I; the QRS vector is thus directed slightly clockwise to the axis of lead 2 ($+60^\circ$). The T vector is directed slightly right of the axis of aVF ($+90^\circ$) since the T wave is slightly negative in lead I and quite positive in lead $\downarrow aVR$.

* The "vectors" shown in Figures 12 and 13 merely indicate the direction of the mean QRS, ST and T forces. Their lengths are not proportional to the actual magnitudes of these forces.

vector marked .04 represents the approximate direction of the mean vector of the first .04 second of the QRS interval and is derived from the Q of .04 duration seen in lead III and aVF and the slurred, wide R of lead aVL . It will be noted that the .04 vector is directed toward approximately -60° whereas the mean frontal QRS vector is at approximately $+60^\circ$. This marked deviation of the initial QRS vectors in direction from that of the mean vector is characteristic of posterior infarction and is due to the unopposed depolarization of the intact opposite wall.²⁴ From this electrocardiogram it is clear that the pathologic Q wave in lead III and in aVF , and the slurred, broad R in aVL are all of the same genesis and related to a distortion of the sequence of depolarization, not to a "window" in the myocardium facing the left leg as has been suggested by Goldberger.²⁵

The electrocardiogram in Figure 13 was taken of the same patient approximately six weeks after his acute attack. The direction of the .04 vector is essentially the same but it has increased in magnitude as shown by the amplitude of R_{aVL} and of Q_3 . The mean QRS vector

has shifted somewhat in a counterclockwise direction. The two striking changes are the disappearance of the injury forces causing the S-T segment deviation and the shift of the T vector approximately 150° in a counterclockwise direction. The .04 second vector and the T vector are now both directed away from the "posterior" or diaphragmatic surface of the heart.

It is apparent that a pathologic Q wave may appear in lead III in posterior infarction without a significant Q_{aVF} , but that the reverse situation cannot occur since the forces (the ".04 vector") which cause a Q_{aVF} also give rise to a Q_3 . Lowen and Pardee²⁶ noted electrocardiograms of patients with posterior infarction which showed an abnormal Q_3 but not an abnormal Q in aVF. They concluded that the bipolar leads were therefore of more value than the augmented unipolar leads in the diagnosis of posterior infarction. Electrocardiograms are occasionally seen from patients with anterior myocardial infarction in which pathologic Q waves appear in aVL without pathologic Q waves in lead I, but the reverse situation does not occur. One might conclude that the augmented unipolar leads were therefore of more value than the bipolar leads in the diagnosis of anterior infarction. When the relative positions of the various lead axes are considered, however, it is apparent that we cannot attribute greater value to bipolar or unipolar leads in the diagnosis of myocardial infarction. The "best lead" or "best leads" will be those whose axes are in the best position to show the characteristic alterations in the initial portion of the time course of the depolarization process.

The electrocardiogram in Figure 14A is that of a healthy, young, hypersthenic male who weighed 200 pounds and was 5 feet 11 inches in height. Roentgenograms and fluoroscopic examination of his chest disclosed the heart to be in a relatively horizontal position. The transitional point for the P vector lies between the axes of aVF ($+90^\circ$) and lead III ($+120^\circ$) at about $+95^\circ$ since the P wave in aVF is diphasic and only very slightly positive and the P in lead III is quite negative; the P vector is at $+5^\circ$. The transitional point for QRS lies approximately at $+75^\circ$ since the positive QRS deflection in lead II is about equal in area to the negative area in lead aVF; the QRS vector is at -15° . The transitional point for T is approximately one-third of the distance between

the axes of aVF and lead III at $+100^\circ$; the T vector lies at $+10^\circ$. It is apparent that the axes of P, QRS and T are all shifted in a counterclockwise direction around an antero-posterior axis and are in normal relation to each other, which is characteristic of the electro-

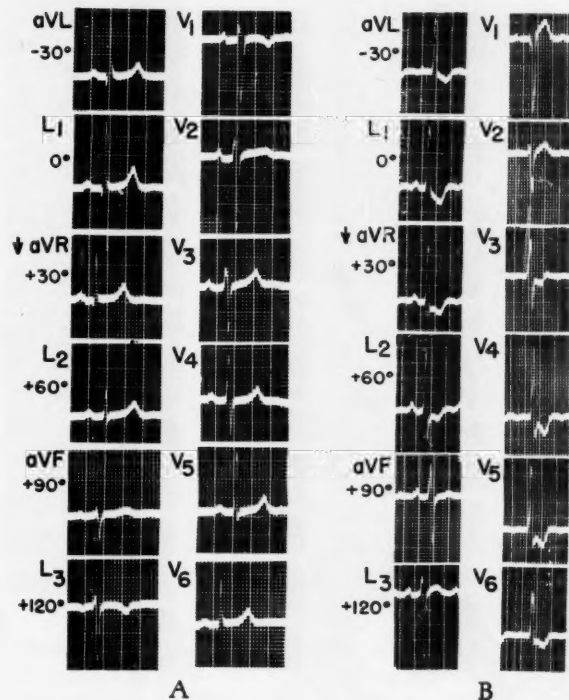


FIG. 14. Electrocardiograms from two patients with "left axis deviation of QRS." A, normal individual with a horizontal heart; B, a patient with left ventricular hypertrophy, with precordial leads recorded at a sensitivity of 1 mv. = 0.5 cm.

cardiogram of many patients with normal, horizontally placed hearts.

The electrocardiogram in Figure 14B was obtained from a middle-aged man of average build who had hypertensive heart disease. Roentgenographic examination revealed moderate left ventricular hypertrophy but the heart was in usual position. The P wave is nearly transitional in form in aVL (-30°) hence the mean P vector is directed toward lead II ($+60^\circ$) which is normal. In lead aVF both the QRS and T waves have a nearly transitional form but the mean QRS vector points toward lead I (0°) and the mean T vector in the opposite direction toward lead I \downarrow (180°). Thus the P, QRS and T vectors are widely separated.

In both of these electrocardiograms "left axis deviation of QRS" is present, -15° in Figure 14A and -5° in Figure 14B. In the first tracing, however, "left axis deviation" of P and

T is also seen and the amplitude of the deflections is normal. The electrocardiogram is entirely within normal limits. In the second tracing the P vector (axis) is in normal position and the T vector shifted markedly to the right. The electrocardiogram thus shows a normal position

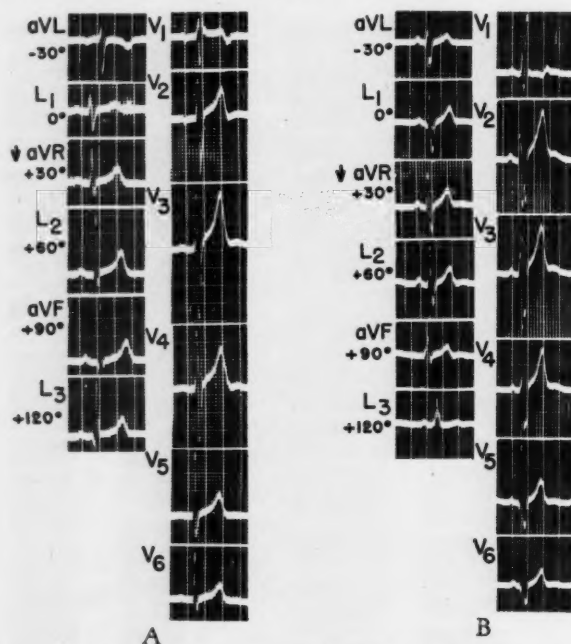


FIG. 15. Electrocardiograms from two patients with "right axis deviation of QRS." A, normal individual with a vertical heart; B, a patient with right ventricular hypertrophy.

of the P vector, a shift of the QRS vector to the left and a marked "right axis deviation" of the T. The amplitude of the QRS deflections is also increased in the extremity and precordial leads (note that the enlargement of the photograph in Figure 14A is considerably greater than that of Figure 14B). The angle between the QRS and T vectors (180°) is markedly increased above normal (0° to 60°), a characteristic finding in most cases of asymmetric ventricular hypertrophy.⁴ The QRS vector points in the direction in the frontal plane of the enlarged ventricle and the T is directed away from it.*

In left ventricular hypertrophy when the characteristic pattern of a tall R wave followed by an inverted T wave appears in lead I, it always appears in lead aVL. (Fig. 14B.) Similarly when a deep S wave followed by an upright T wave appears in aVF in left ventricular hypertrophy, the complex in lead III will have the same general configuration. The character-

* Since the QRS-T angle is 180° , the ventricular gradient is zero in the frontal plane.

istic pattern of a tall R with an inverted T may appear only in aVL, with an isoelectric T in lead I, however, if the T vector is not rotated far enough in a clockwise direction to produce an inversion of T_1 as well as of T_{aVL} . Similarly the QRS pattern of left ventricular hypertrophy (small R, deep S) may appear only in lead III, not in aVF, if the QRS vector is not rotated far enough in a counterclockwise direction to produce a negative complex in aVF.

The two electrocardiograms in Figure 15 illustrate two examples of "right axis deviation." The first tracing is that of a healthy twenty year old boy whose height was 6 feet and whose weight was 120 pounds. Roentgenograms showed a vertically placed heart of normal size. The transitional point for the P vector is at about -10° ; the P vector is directed toward $+80^\circ$. The transitional point for QRS is at $+5^\circ$ and that for T at -10° , hence the QRS vector lies at $+95^\circ$ and the T vector at $+80^\circ$. The QRS interval in the extremity leads is slightly over .09 second and that in the precordial leads slightly over .10 second. An RR' pattern appears in the V_1 position. This type of electrocardiogram has been seen not infrequently in normal young individuals²⁷ and is not believed to represent incomplete right bundle branch block.

In the tracing shown in Figure 15B the transitional point for the P vector is at $+130^\circ$ (the flat P in aVF is an artifact), the P vector at $+40^\circ$. The QRS transitional point is between the axes of leads I and \downarrow aVR, closer to $+30^\circ$ than to 0° because of the greater area of the S_1 than the R_1 and the almost equal area of R and S in \downarrow aVR, thus the QRS vector is at approximately ($+110$ to $+115^\circ$). The transitional point for T is at $+130^\circ$, T vector directed at $+40^\circ$. The QRS interval is slightly less than .12 second in the extremity leads and .12 second in the precordial leads. A broad, deep S wave in leads aVL, I, and V_4 , V_5 and V_6 , and the greater positive area of QRS in the right precordial leads than the left with the RR' pattern in V_1 are compatible with the diagnosis of incomplete right bundle branch block of the type which is occasionally seen in right ventricular hypertrophy. This patient had pulmonic stenosis with right ventricular hypertrophy and a normal position of the heart on roentgenographic examination.

In the first of these two electrocardiograms the P, QRS and T vectors are all shifted to the right as is frequently the case when the heart

rotates on its anteroposterior axis in a clockwise direction. In the second the P vector is in normal position, the QRS vector is increased in magnitude and shifted toward the right ventricle in the frontal plane and the T vector somewhat deviated away from the right ventricle. These changes are consistent with the diagnosis of right ventricular hypertrophy and incomplete right bundle branch block.^{4,10}

In Figure 16 is shown the electrocardiogram of a young woman with no history or symptoms suggesting cardiovascular disease. The transitional point for the P vector is at $+30^\circ$, the P vector at $+120^\circ$, that for QRS at $+15^\circ$ with the QRS vector at $+105^\circ$, and the transitional point for T is at $+75^\circ$ with the T vector directed at $+165^\circ$. The relationship of the P, QRS and T vectors to each other is normal but they are all directed toward the right chest. The precordial leads indicate the presence of dextrocardia which was confirmed by the roentgenographic examination.

COMMENTS

Since the introduction of the central terminal by Wilson²⁸ in 1934 and the subsequent presentation of methods of augmenting the potentials recorded in unipolar leads by Goldberger¹⁶ in 1942, the unipolar and augmented unipolar extremity leads have become widely used in electrocardiography. Connections necessary for recording the augmented unipolar leads are now incorporated in most electrocardiographs. The bipolar and unipolar extremity leads are commonly mounted separately and interpreted according to different criteria and are regarded as being of different significance in the interpretation of the electrocardiogram. It is thought by several observers that the unipolar leads are of considerably more value than the bipolar leads; indeed Myers²⁹ states that since there is no information to be obtained from bipolar leads which cannot be obtained from the unipolar leads the former need only be taken for purposes of comparison in patients who had electrocardiograms made in the era prior to the introduction of the unipolar leads. Goldberger²⁵ believes that since the bipolar leads give less information than the unipolar leads, the former need not be recorded. Wolferth, Livesey and Wood³⁰ have also concluded that the bipolar leads need no longer be taken.

Proposals that the bipolar leads are no longer useful minimize the relationship of all the ex-

trinity leads to the total electric field of the heart and seem to imply that the complexes seen in the unipolar leads represent other than different projections of the mean electric forces produced in the body by the spread of excitation through the heart. The tendency toward

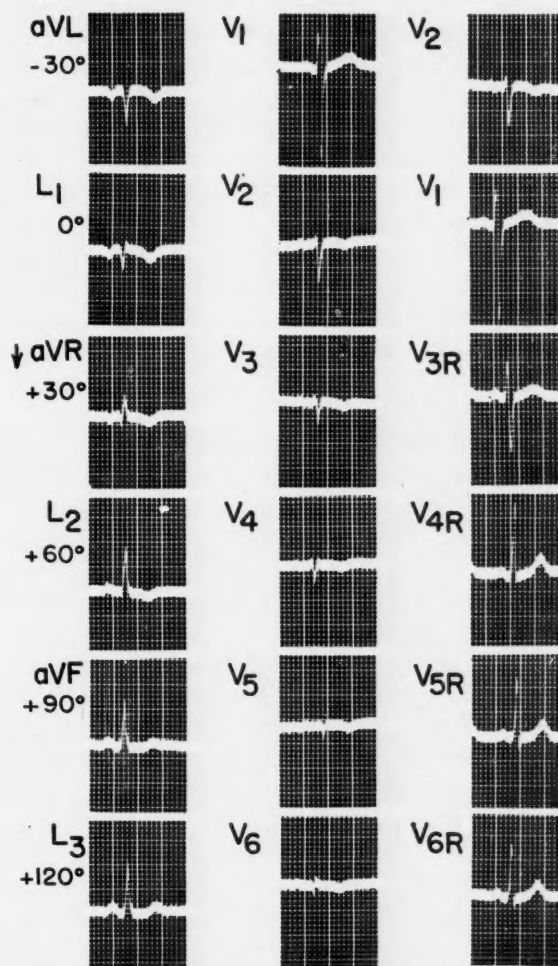


FIG. 16. Electrocardiogram from a normal young woman with dextrocardia.

discarding the bipolar leads seems to us to be unfortunate for clinical electrocardiography since many physicians are familiar only with common patterns seen in the bipolar leads in association with certain myocardial abnormalities. In most courses in electrocardiography, moreover, an empiric approach derived from the standard limb leads is employed.

When the direction and relative magnitude of the deflections in the extremity leads are regarded from the point of view of their relation to the electric field of the heart at successive instants during the cardiac cycle, it is obvious that greater value in electrocardiographic inter-

pretation cannot be ascribed to either bipolar or unipolar extremity leads since each extremity lead gives a different "view" of the mean electric field of the heart in the frontal plane.

It is also clear that the inter-relation of all extremity leads becomes immediately apparent and that considerably more information can be easily obtained concerning the variations in orientation and magnitude of the electric field during the cardiac cycle if the polarity of the right arm unipolar lead is reversed during the recording of the electrocardiogram or if six additional leads with reversed polarity are made and the tracings mounted according to the angles their axes make with that of lead I. These variations can be best appreciated if all twelve leads are taken but are readily apparent if only six leads, including the reversed right arm unipolar lead, are recorded and appropriately mounted.

A precedent for the reversal of the polarity of the right arm unipolar lead was established by Einthoven when he reversed the polarity of the bipolar lead recorded from the right arm and left leg, i.e., lead II.³¹ Since the mean frontal QRS vector is directed in a base-apex direction in normal hearts and thus points downward and to the left, usually more nearly parallel with the axis of lead II (+60°) than with the axis of either lead I or lead III, the greatest deflection in the standard limb leads is commonly seen in lead II. Einthoven reversed the polarity of the connections of the galvanometer to the right arm and left leg when recording the second lead in order that the complexes in the three standard leads would be upright in most electrocardiograms.

The similarities between the considerations which led Einthoven to reverse the polarity of lead II and the considerations which led us to reverse the polarity of the right arm unipolar lead are obvious. The mean frontal QRS vector is usually more nearly parallel to the axis of VR than the axes of either VL or VF, but the deflection in lead VR is normally inverted. The negative portion of axis of lead II and the positive axis of VR as usually recorded lie at -120° and -150°, respectively, on the hexaxial system. The relative stability of aVR has been emphasized.^{1,29} Although the complexes in VL and VF, like those of lead I and lead III, vary markedly with changes in the relation of the electric field of the heart to the extremity electrodes, VR, like lead II, is relatively more stable

and might be termed the "axis lead" of the unipolar extremity leads for the same reasons that lead II is regarded as the "axis lead" of the standard limb leads. It seemed logical, therefore, to reverse the polarity of the right arm lead when recording the electrocardiogram.* This can be done simply by reversing the wiring within the lead selector switch in such manner that the right arm electrode is connected to the negative lead of the amplifier and the positive lead of the amplifier connected to the central terminal when recording the unipolar right arm lead. A double pole, double throw switch attached to the right and left arm wires from the amplifier to a lead selector box will accomplish the same purpose and, furthermore, facilitate the recording of other leads with reversed polarity.

The reversal of polarity of the right arm lead in no manner interferes with interpretation of the electrocardiogram according to the data which have been accumulated concerning the configuration of the complexes in VR or aVR as usually recorded. The initial R of aVR, for example, is caused by the same forces which cause a Q₁ or Q₂ and an S_{aVR} is of the same genesis as the R₁ or R₂. The frequent occurrence of a small Q wave followed by a tall R wave in a VR ventricular hypertrophy has been emphasized by Myers.³² This qR pattern of aVR is the same as the rS pattern in ↓aVR and is clearly caused by the clockwise rotation of the QRS forces which usually occurs with right ventricular hypertrophy and which is responsible for the rS pattern in lead I.

The mathematical relationships of the amplitude of the deflections recorded in the bipolar and various unipolar leads are familiar, as is the fact that the configuration of the complex seen in a bipolar lead represents the algebraic difference of potential variation occurring in two unipolar leads during the cardiac cycle. Little attention has been given, however, to the common relationship of the configuration and magnitude of the deflections seen in both the unipolar and bipolar leads to the electric field of the heart. The relatively small amplitude of the deflections in the ordinary unipolar leads compared with those in the bipolar leads and the

* The relation of the potentials recorded in the unipolar leads when the polarity of VR is reversed is similar to that of the bipolar leads, $L_1 + L_3 = L_2$:

$$\begin{array}{ll} VL + (-VR) + VF = 0 & aVL + aVF = \downarrow aVR \\ VL + VF = \downarrow VR & vVL + vVF = \downarrow vVR \end{array}$$

common practice of mounting bipolar and unipolar leads separately have made it difficult to visualize the vector relationships of the extremity leads by inspection of the tracing. Thus in order to facilitate the routine study of electrocardiograms by vector methods, or the interpretation of tracings by any method, it is desirable to make deflections in the unipolar leads more nearly comparable in magnitude to those of the bipolar leads in addition to changing the technics of mounting the tracings.

Amplification of the unipolar leads because of their small deflections relative to those of the bipolar leads is a common practice. The Goldberger¹⁶ technic of disconnecting the lead wire from the central terminal to the limb from which the unipolar lead is being recorded theoretically results in an increased amplitude of 50 per cent, which is adequate for routine use.* Augmentation of the unipolar leads is also frequently obtained by increasing the amplification of the electrocardiograph to 1 mv. = 15 mm. or 1 mv. = 20 mm. with the Wilson central terminal. In order to make the bipolar and unipolar leads entirely comparable, i.e., to make the amplitudes and areas of the deflections in the six extremity leads proportional to the projections of a cardiac vector on the axes of the six leads, the sensitivity of the electrocardiograph machine should be set at 1 mv. = 17.3 mm. when the unipolar leads are recorded. The leads obtained in this manner, which we have called the vector unipolar leads, are of considerable value in the study of the frontal and sagittal plane vectorcardiogram, in the study of the ventricular gradient and for teaching purposes, but the extra steps necessary to record them preclude their routine use in clinical electrocardiography at present.

The validity of the hexaxial reference system and the vector unipolar leads depends, of course, on the accuracy of the Einthoven hypothesis. Since Einthoven's assumptions only closely approximate the actual relation of the electric field of the heart to the potentials at the surface of the body¹⁰⁻¹² and since slight potential variation of the central terminal must therefore occur, the technics for unification of the bipolar and unipolar extremity leads can only result in an

approximate equivalence of all extremity leads with respect to the electric field of the heart. The step-like sequence in wave form and area of the deflections in adjacent vector unipolar and bipolar leads and the fact that a mean cardiac vector may be derived either from the bipolar or vector unipolar leads (Fig. 5), however, are attributable to the essential validity of Einthoven's assumptions.

The sequential change in configuration and amplitude of the P, Q, R, S and T deflections in the six extremity leads aVL to lead III is similar to that seen in the precordial leads V1 to V6. In Figure 15A, for example, the sequence of the configuration of the complexes in the extremity leads strongly resembles that seen in precordial leads. The studies of Duchosal,³⁸ Spang³⁵ and Grant^{4,7,36,37} have shown that the configuration of the complexes in precordial leads and other leads recorded from the trunk may be analyzed in a manner similar to that used in the study of the extremity leads, i.e., they may be related to the projection of the spatial cardiac vector on their axes, and Grant⁶ has recently presented methods for determination of the spatial orientation of the electric forces of the heart.

When the relation of the cardiac vector to the configuration of the complex in any electrocardiographic lead is considered, it becomes apparent that all leads are actually "bipolar" leads. The spatial orientation of the axis of any lead with respect to other lead axes is determined by two points, not by one point. Although the complex obtained at a particular point on the body by the use of the central terminal is considered as representing the potential variation at that point, it is also "bipolar" in the sense that the potential difference between two points is being measured, as pointed out by Spang.³⁵ The distinction between "bipolar" and "unipolar" leads is useful only if tracings could be obtained which represented the potential variation of only a small area of the epicardium. The studies of the spatial electrocardiogram and vectorcardiogram mentioned heretofore have shown that although the amplitude of the complexes in the precordial leads is greatly influenced by proximity of the electrode to the epicardium the configuration of the complexes is less influenced and is caused largely by variations in the orientation and magnitude of the entire electric field of the heart, not predominantly by the electric events of the

* As has been shown by Rappaport and Williams,¹¹ Bryant and Johnson,³³ and Simonson and Keys,³⁴ the augmentation of the unipolar leads obtained by the Goldberger technic or the Goldberger modification of the Wilson technic is not always 50 per cent.

underlying portion of the ventricular wall. If this is true, determination of the actual potential variation in the precordial and, of course, extremity leads, becomes of considerably less clinical importance than the determination of the vector projections on the axes of the precordial and extremity leads. It also follows that electrocardiographic technics should be devised in which an equivalent amplitude of deflection in all leads, taken from the extremities or from the trunk, should be produced by the cardiac vector. The present paper illustrates how this may be accomplished in the extremity leads. Subsequent reports will concern methods of recording leads from the trunk which are equivalent to the extremity leads.

It is hoped that by the use of such leads the spatial orientation and magnitude of the QRS forces and the ventricular gradient may be determined and related by inspection of the electrocardiogram. Furthermore, if the spatial orientation of the electric forces produced by depolarization and repolarization can be visualized easily by the use of a few appropriately recorded leads, clinical electrocardiography may be considerably simplified.

SUMMARY

1. The relationships of the axes and amplitudes of the deflections of the bipolar and unipolar leads have been reviewed.

2. By appropriately increasing the sensitivity of the recorder unipolar limb leads were obtained in which the amplitude and areas of the deflections were equivalent to those obtained from mensuration of the bipolar leads with respect to the magnitude of the cardiac vector.

3. By reversing the polarity of the connections between patient and recorder six additional curves of reciprocal form were obtained. When the twelve curves were properly arranged, they represented twelve different "views" of the electric field of the heart in the frontal plane.

4. Such an arrangement offers the following advantages: (1) the relationship between the bipolar and unipolar limb leads immediately becomes clear; (2) the transitions in form of P, QRS and T around the entire electric field can be readily observed and measured; (3) estimation of the mean vectors of P, QRS and T in the frontal plane can be done by inspection; and (4) the changes in direction of the excitation wave during the depolarization process can be estimated.

5. Most of these advantages are gained if the following modifications are made in the present day procedure. First, reverse the polarity in obtaining the unipolar right arm lead; second, mount the six limb leads in the following sequence from above downward; aVL, lead I, aVR (polarity reversed), lead II, aVF and lead III.

6. Illustrations are given of some of the advantages to clinical electrocardiography.

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The Exercise Electrocardiogram*

An Aid in the Diagnosis of Arteriosclerotic Heart Disease in Persons Exhibiting Abnormally Large Q₃ Waves

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METHODS of differentiating normal from abnormal Q waves in lead III have been subjected to considerable in-

vestigation. Pardee, in 1930, proposed a criterion for a diagnostically significant Q₃: An initial deflection of more than 25 per cent of the

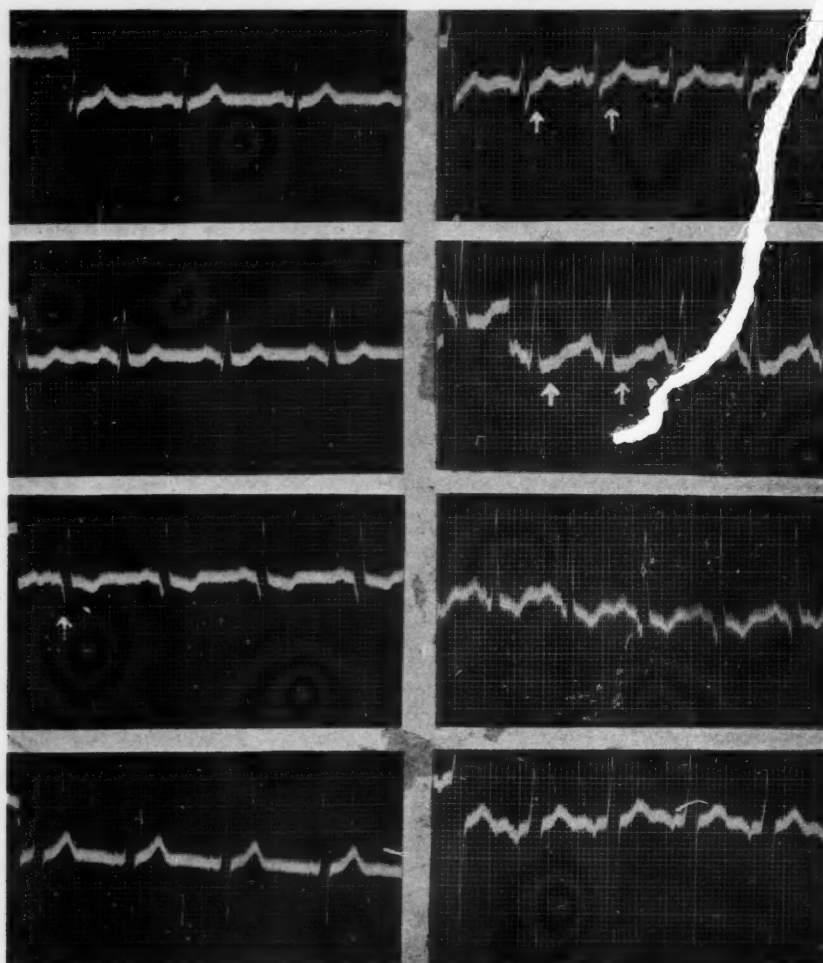


FIG. 1. White male, age sixty; history of myocardial infarction; asymptomatic three years. Physical examination: slightly obese, hypersthenic type of chest, blood pressure 140/80, no evidence of cardiac enlargement. Electrocardiogram (A) before exercise: large Q and inverted T waves in lead III. Electrocardiogram (B) after exercise: depressed S-T segment in leads I, II and III. Diagnosis: coronary artery insufficiency.

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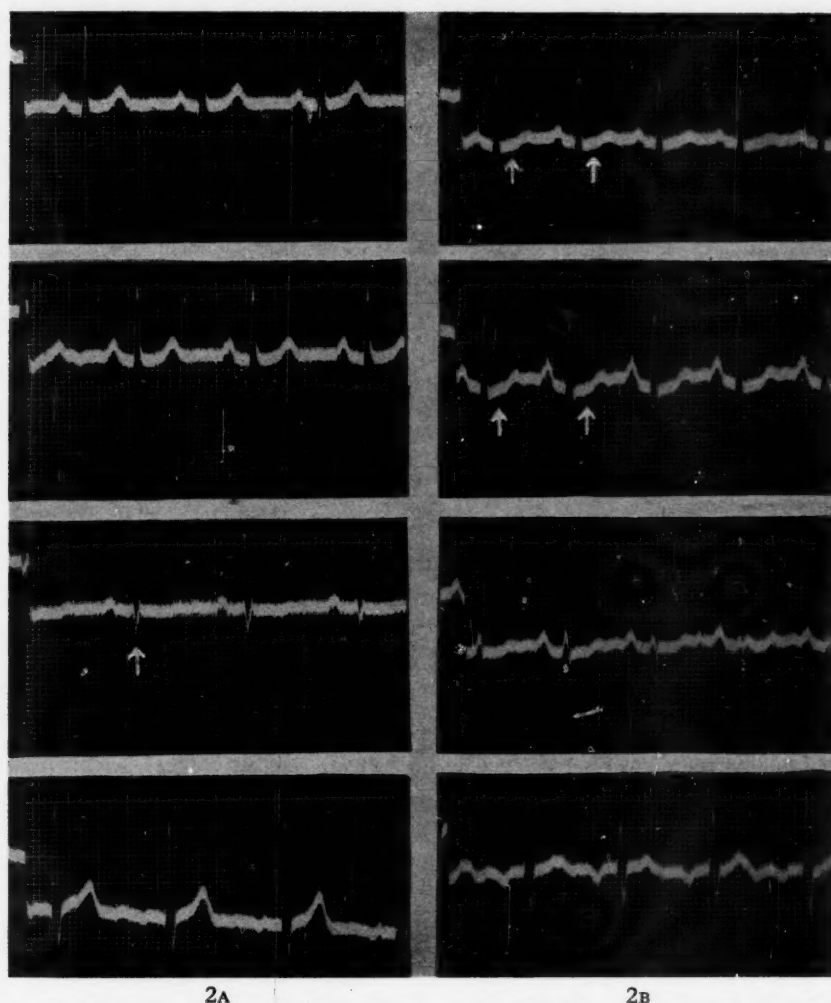


FIG. 2. White male, age fifty-five; history suggestive of angina pectoris. Physical examination: average build, blood pressure 150/85, no evidence of cardiac enlargement. Electrocardiogram (A) before exercise: large Q and iso-electric T waves in lead III. Electrocardiogram (B) after exercise: depressed S-T segment in leads I and II, diphasic (— +) T waves in lead III. Diagnosis: angina pectoris with coronary insufficiency.

greatest excursion of the QRS complex in any standard lead in electrocardiograms that did not exhibit right axis deviation or notched (M or W) complexes. He considered this presumptive evidence of coronary artery disease in the majority of cases.

Several authors²⁻⁵ have since compiled electrocardiograms in a large number of normal hearts and by this standard the total incidence of a significant Q_3 was determined to be less than 1 per cent. Electrocardiograms made on normal hearts in men in military service⁶ revealed an increase in this percentage indicating that other methods may be desirable to establish the abnormality of a large Q_3 .

Master and his associates⁷ have devised an exercise test of cardiac function that utilizes the

electrocardiogram: After exercise a depression of the RS-T segment of more than 0.5 mm. in any lead and a T wave that becomes iso-electric or inverted or changes direction is regarded as evidence of coronary artery disease. These standards have been modified by others.^{8,9} The criteria used in the present study were an RS-T segment depression of at least 1 mm. in lead I or 1.5 mm. in lead II, or 2 mm. in lead III, or a T wave change as Master proposed for lead III for a "positive" exercise electrocardiogram as evidence of arteriosclerotic heart disease.

MATERIAL

Twenty persons with the single abnormality of a large Q wave in lead III were subjected to the Master "two-step" test and electrocardio-

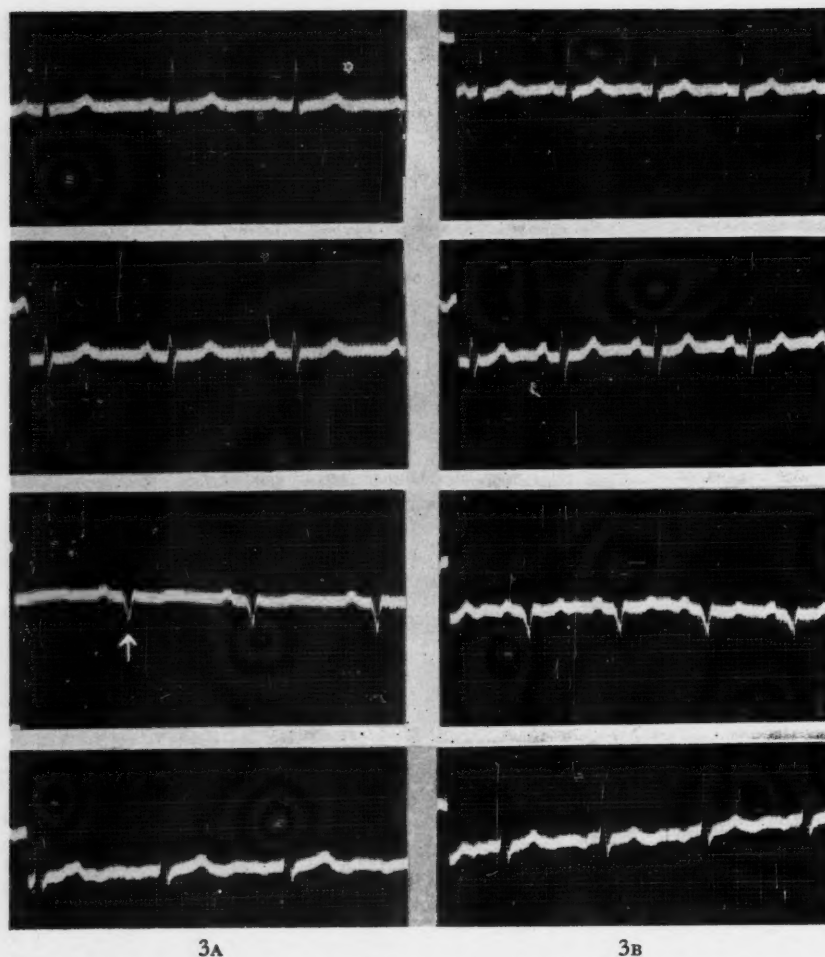


FIG. 3. White male, age sixty-three; history negative for coronary artery disease. Physical examination: average build, blood pressure 130/80, no evidence of cardiac enlargement. Electrocardiogram (A) before exercise: large Q and isoelectric T waves in lead III. Electrocardiogram (B) after exercise: no alteration except slightly upright T waves in lead III. Diagnosis: normal electrocardiogram, no evidence of latent coronary artery insufficiency.

grams were recorded immediately after exercise and five minutes later. Ten patients had previously had myocardial infarction from one to five years prior to this examination. There was no clinical evidence of previous myocardial infarction in the other patients. The exercise electrocardiogram was "positive" in five persons with a previous myocardial infarction (Figs. 1 and 2) and "negative" or unaltered in all of those without other evidence of previous infarction. (Fig. 3.)

The large Q_s wave occurring in an electrocardiogram in persons with normal hearts has been stated to be due to rotation of the heart to the left by an elevated diaphragm.^{1,3,10-12} This may be present if there is a hypersthenic type of chest or in conditions that produce abdominal distention.^{5,11} The size of the Q_s is affected by

respiration; it becoming larger during expiration and smaller during inspiration.^{1,11}

Excessive exercise in normal persons may cause alterations in the ST segment and T waves. These are transient, disappear with a decrease in heart rate and have been stated to be due to reduction in coronary artery circulation incident to tachycardia.¹³

Abnormal conditions, other than coronary arteriosclerosis that may produce a large Q_s , are chronic hypertensive or chronic valvular heart disease.^{1,14,15} A large Q_s is associated as frequently with hypertension uncomplicated by angina as with coronary artery insufficiency. Persons with hypertension may be studied by the exercise electrocardiogram for evidence of coronary artery insufficiency. (Fig. 4.)

The large Q_s wave is usually permanent evi-

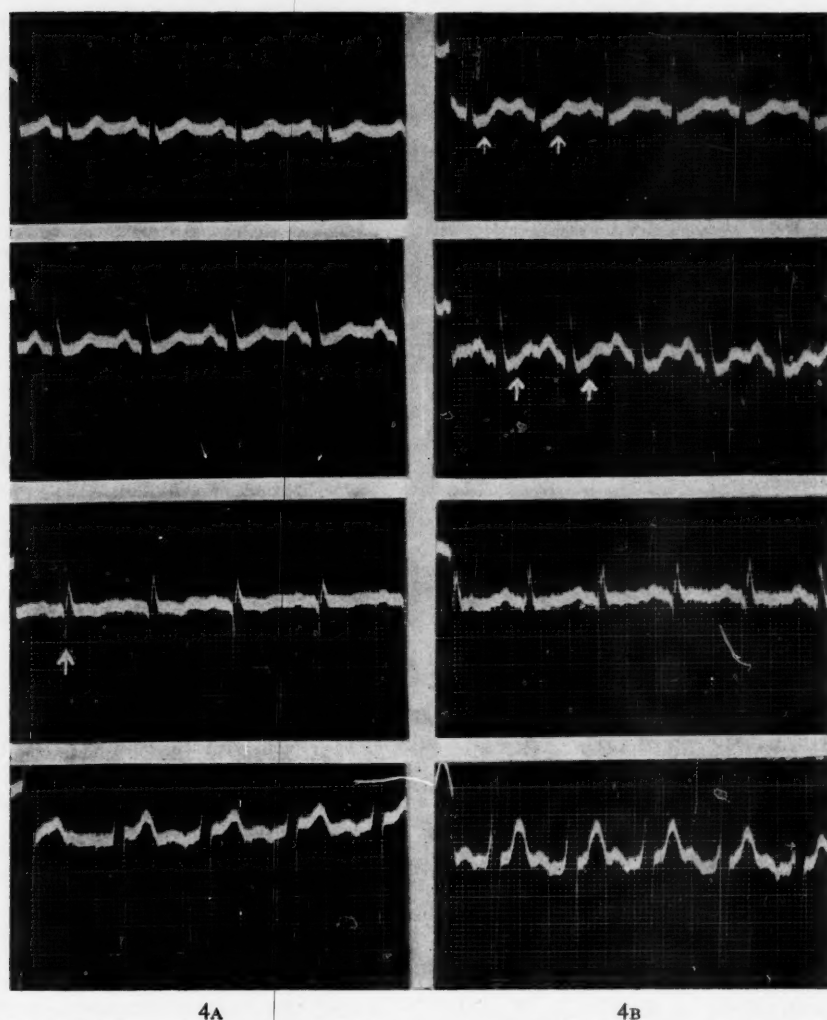


FIG. 4. White male, age forty-five; history not conclusive for coronary artery disease. Physical examination: slightly obese, hypersthenic type of chest, blood pressure 200/100, moderate cardiac enlargement. Electrocardiogram (A) before exercise: large Q and inverted T waves in lead III. Electrocardiogram (B) after exercise: depressed S-T segment in leads I and II, iso-electric T waves in lead III. Diagnosis: latent coronary artery insufficiency.

dence of a former posterior myocardial infarction after other electrocardiographic signs have disappeared. This study indicates that a "positive" exercise electrocardiogram is fairly reliable evidence of coronary artery insufficiency in patients with no other alteration than a large Q_3 in the routine electrocardiogram. The results in each patient were the same when the tests were repeated at the end of one year from the original exercise test.

It is recognized that in some persons a positive test may become negative after an interval of time. This has been stated to be due, in part, to functional influence but may also be due to development of a sufficient collateral circulation. Coronary arteriosclerosis is not a constantly

progressive condition; and according to Biorck¹⁶ a stable positive test may be a more favorable sign than one that later becomes negative, for the latter may indicate either an active sclerotic process or a functional instability, both equally undesirable.

The fact that the patients studied had a positive test one year after posterior myocardial infarction may indicate a decreased potentiality for a collateral circulation after infarction in this region. Further studies of the exercise electrocardiogram after posterior infarction should be made at this minimum interval of time.

Goldberger¹⁷ and others^{18,19} have demonstrated the value of the unipolar electrocardiogram in differentiating a normal from an

abnormal Q_s wave. The exercise electrocardiogram may also be of aid in the diagnosis of arteriosclerotic heart disease in persons exhibiting abnormally large Q_s waves.

SUMMARY

Twenty persons with the single electrocardiographic abnormality of a large Q wave in lead III were studied by the exercise electrocardiogram.

In five persons who had a previous myocardial infarction the exercise electrocardiogram was "positive" and remained so through a minimum period of one year after recovery.

In the others who had no clinical evidence of previous infarction the exercise electrocardiogram was "negative" or unaltered.

The significance of these results is discussed in relation to the diagnosis of arteriosclerotic heart disease.

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Clinical and Cardiac Catheterization Studies in Four Cases of Eisenmenger's Complex*

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THE purpose of this communication is to evaluate the clinical and cardiac catheterization criteria in Eisenmenger's complex. Since the original publication of Eisenmenger¹ only a few cases having this abnormality have been reported in detail.²⁻⁵

The complex of Eisenmenger consists of a high ventricular septal defect, an aorta which overrides both the right and left ventricles (dextroposition of the aorta), right ventricular hypertrophy and a dilated pulmonary artery. In addition to the abnormal position of the aorta there is often an abnormality of the aortic valve and upward displacement of the coronary ostia may occur.²

The onset of cyanosis in childhood or adolescence is probably the most important single point in the history in Eisenmenger's complex. However, there are occasional cases in which cyanosis may date from birth. Cyanosis is usually less marked than in tetralogy of Fallot, as is the clubbing of fingers and toes. Clubbing usually follows the onset of cyanosis by several years. Shortness of breath is not a striking symptom although all patients show some limitation of cardiac reserve on careful questioning. Growth and development are usually normal. These latter factors are probably related to the very mild degree of anoxia during childhood and adolescence. The presence or absence of "squatting" (a characteristic symptom in tetralogy of Fallot) does not seem of diagnostic impor-

tance since squatting was present in two of Bing's five cases³ and is not mentioned in other clinical studies. Hemoptyses occasionally occur and probably are related to the excessive pulmonary flow. Hoarseness and a brassy cough may occur.²

Clinically, the heart size is most often within the normal range. Cardiac hypertrophy is right ventricular in type and is thus not readily detected on physical examination. Blood pressure is not abnormal. The heart sounds are normal except for a very characteristic and uniform accentuation of the pulmonic second sound. A systolic murmur over the base of the heart is usually present. It varies considerably in intensity and character, at times being harsh and loud and at other times soft and minimal in intensity. A systolic thrill may be felt when the murmur is of maximum intensity. The murmur and thrill are explicable on the basis of the overriding aorta and may be transmitted throughout the arterial tree.

Occasionally a diastolic murmur is heard along the left sternal border. In certain situations it seems likely that this represents aortic insufficiency since it is accompanied with peripheral signs of aortic regurgitation. The cause for this does not seem evident although Taussig mentions that it may be due to the unequal size of the three aortic cusps. However, pulmonary insufficiency may also be present, producing a murmur of lesser intensity along the left sternal border, and we have seen one patient in

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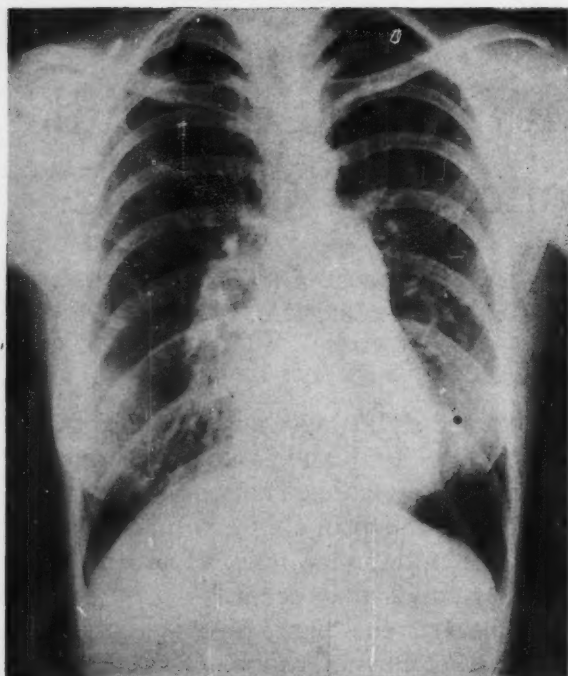


FIG. 1. A, orthodiagram of Case 1 showing prominent pulmonary arteries.

whom it appeared that two diastolic murmurs of variable pitch and intensity were present.

The x-ray configuration of the heart itself does not appear characteristic. The size on fluoroscopy may be normal or slightly enlarged. The pulmonary arc may be prominent in the anteroposterior position and in the right oblique. In the older patient and with slight cardiac enlargement the pulmonary vascular shadows are prominent. Expansile pulsation of the pulmonary arteries is often present. The electrocardiogram shows right axis deviation, with right ventricular hypertrophy. This has been uniform in our experience but one of Bing's cases,³ a patient with a large heart, showed left axis deviation.

Taussig has stated,² "An Eisenmenger's complex is one of the few malformations which require additional laboratory studies in order to make definite clinical diagnosis." The following determinations will allow a complete and accurate laboratory diagnosis: (1) Hypertrophy of the right ventricle and pulmonary hypertension may be determined accurately by cardiac catheterization. (2)

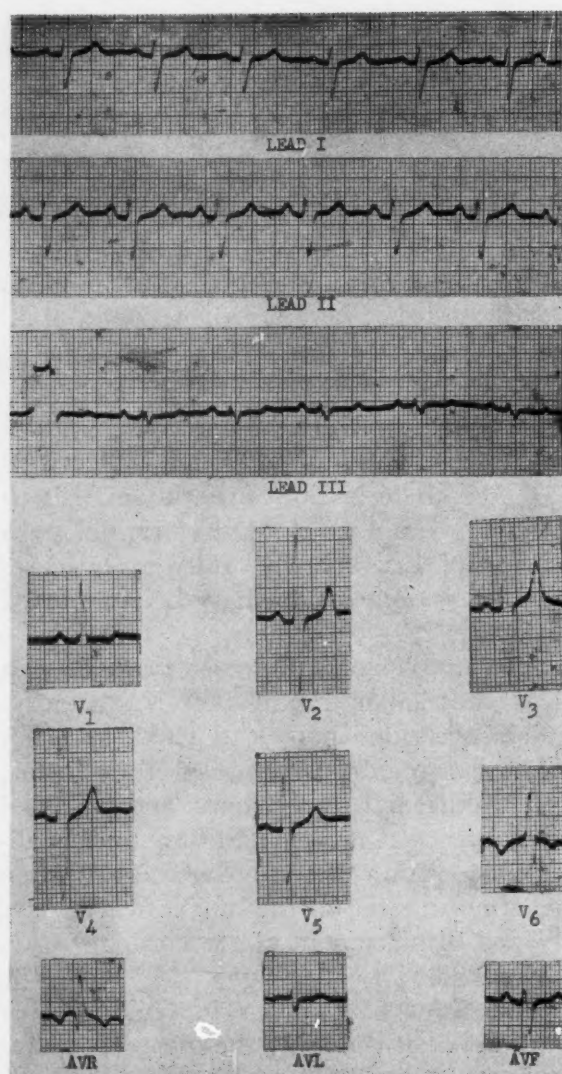


FIG. 1. B, electrocardiogram of Case 1 showing right ventricular hypertrophy.

Information relative to overriding of the aorta may be secured by several methods; the cardiac catheter may be passed from the right ventricle directly into the aorta; the arm-to-tongue circulation time may be abnormally short; diodrast may be seen to pass directly from the right ventricle into the aorta, and finally, as will be shown, by analysis of oxygen and pressure relationships. (3) A high ventricular septal defect may be demonstrated by the presence of increased oxygenation in the upper portion of the right ventricle or pulmonary artery or by passage of the catheter through the defect. Thus it will be seen that each of the abnormalities comprising the Eisenmenger's

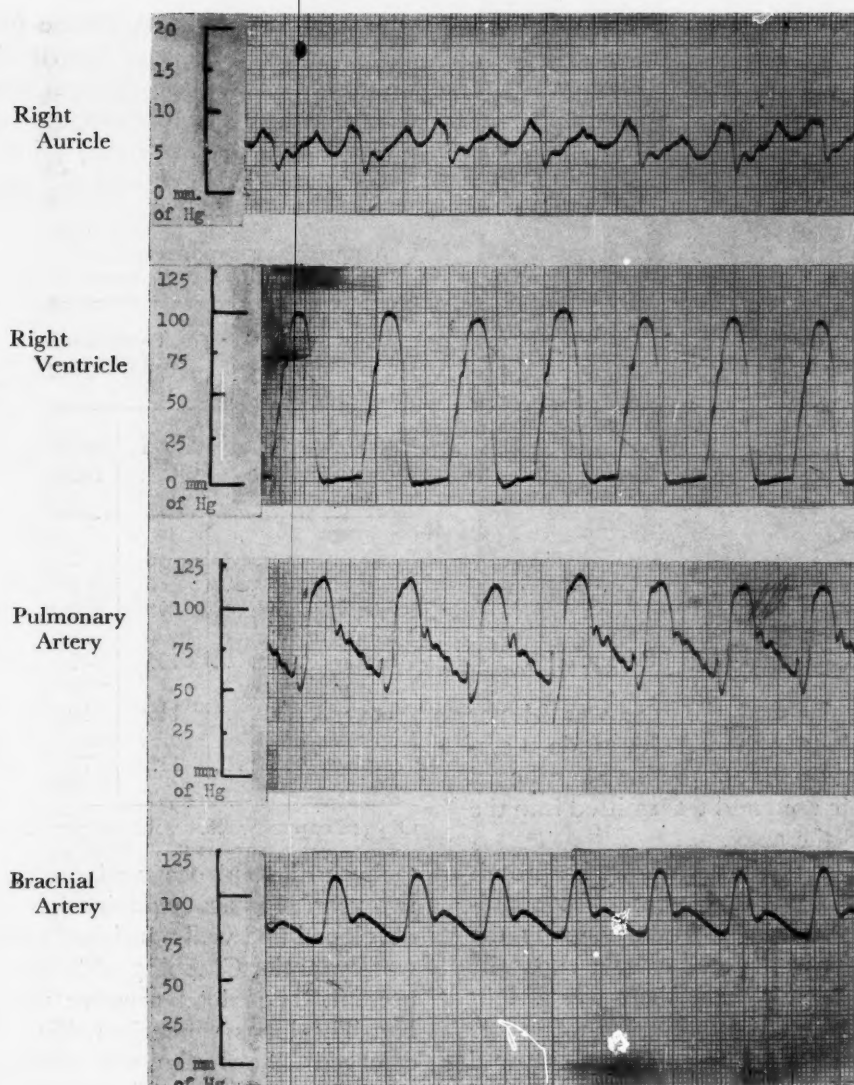


FIG. 1. c, intracardiac and intravascular pressures in Case 1.

complex is subject to reasonably accurate determination by one or more of the special methods we have outlined. In addition, following a standard exercise test the oxygen consumed per liter of ventilation rises, in contrast to a fall in oxygen after exercise in tetralogy of Fallot.

Four patients with Eisenmenger's complex were studied by cardiac catheterization. Under local anesthesia the cardiac catheter was introduced into a branch of the left median basilic vein and passed successively into the superior vena cava, right auricle, right ventricle and pulmonary artery. Oxygen samples were obtained and analyzed by the Van Slyke method. Pres-

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ures were measured by either a water manometer, an electromanometer or by a strain gage. An inlying arterial needle was used to record intra-arterial pressures and obtain arterial blood samples.

CASE REPORTS

CASE 1. A twenty-nine year old white female, cyanotic since thirteen, was admitted for cardiac catheterization. Following the onset of cyanosis, clubbing of the fingers and toes developed. Dyspnea was present on marked exertion. Physical examination revealed a well developed white female with cyanosis of the skin and mucous membranes. Clubbing of the fingers and toes was present. The blood pressure was 100/78 mm. Hg. The heart was not enlarged. The

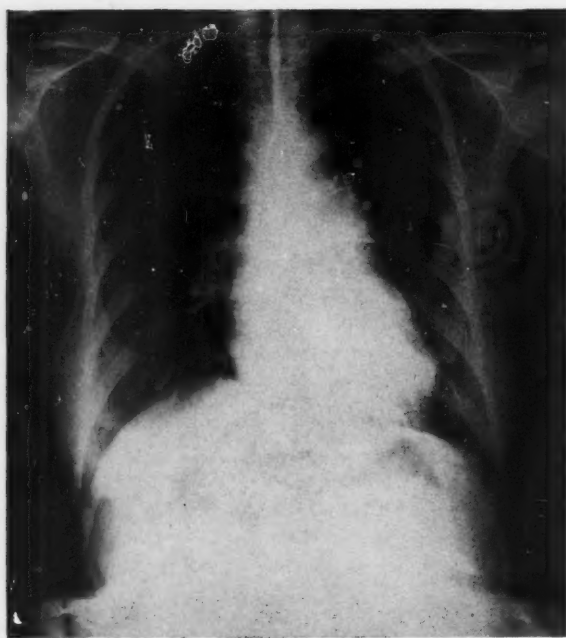


FIG. 2. A, orthodiagram of Case II.

rhythm was regular and the rate was 84 per minute. P_2 was louder than A_2 . A grade II systolic murmur was present at the base best heard over the pulmonic area and transmitted into the neck and toward the apex.

X-ray of the heart (Fig. 1A) showed a prominent pulmonary arc with increase of the pulmonary arterial markings. At fluoroscopy the pulmonary arteries were noted to have expansile pulsations. In the left oblique there was a right auricular shelf and the right ventricle was grade II enlarged. The electrocardiogram showed right ventricular hypertrophy. (Fig. 1B.)

The hemoglobin was 19.5 gm. The red blood count was 6.8 million. The arm-to-tongue circulation time (decholin) was twelve seconds, and the arm-to-lung circulation time (ether) was eight seconds.

Data obtained by cardiac catheterization are summarized in Table I. The increase of 1.6 volumes per cent in oxygen content in passing from the right ventricle to the pulmonary artery is significant and probably represents a left-to-right shunt through a high ventricular septal defect. Pressure studies (Fig. 1C) showed right ventricular systolic hypertension (99/2 mm. Hg). In the pulmonary artery there was both systolic and diastolic hypertension (115/50 mm. Hg). These tracings were not simultaneously recorded. It was not possible to obtain evidence of overriding of the aorta.

CASE II. A forty-three year old white female

with a history of heart disease from birth was admitted for cardiac catheterization. Cyanosis was said to have been present from birth, and clubbing of the fingers and toes as long as the patient could remember. Dyspnea on effort had been observed. Two attacks of paroxysmal

TABLE I
CARDIAC CATHETERIZATION STUDIES IN TETRALOGY
OF EISENMENGER—CASE I

Station	Pressure (mm. Hg)		Oxygen Content (Vol- umes Per cent)	Per cent Oxygen Satura- tion
	Sys- tolic	Dias- tolic		
Superior vena cava	6	2	14.7	55.7
Right atrium.....	6	2	15.5	58.8
Right ventricle....	99	2	16.0	60.6
Main pulmonary artery.....	105	45	17.6	70.6
Right pulmonary artery.....	115	50	17.8	76.5
Right brachial artery.....	115	75	21.8	82.7

Oxygen capacity: 26.4 volumes per cent

tachycardia had occurred during the previous two years. Physical examination revealed a well developed and well nourished white female who was cyanotic. Clubbing of fingers and toes was present. The blood pressure was 125/85 mm. Hg. The lungs were clear. The heart was not enlarged. The rhythm was regular and the rate was 75 per minute. The sounds were of good quality. P_2 was accentuated. A grade I pulmonary systolic murmur and a grade II basal diastolic murmur best heard in the second and third interspaces to the left of the sternum were present. One observer thought that there were two different diastolic murmurs along the left sternal border.

X-ray of the heart (Fig. 2A) showed a normal heart size with no definitive chamber enlargement. At fluoroscopy the pulmonary arteries were observed to have an expansile pulsation. The electrocardiogram (Fig. 2B) showed right ventricular hypertrophy. The red blood count was 6.8 million; the hemoglobin was 23 gm. Data obtained by cardiac catheterization are summarized in Table II. On passing from the right ventricle to the main pulmonary artery the oxygen content increased 1.4 volumes per cent, indicating a high interventricular septal

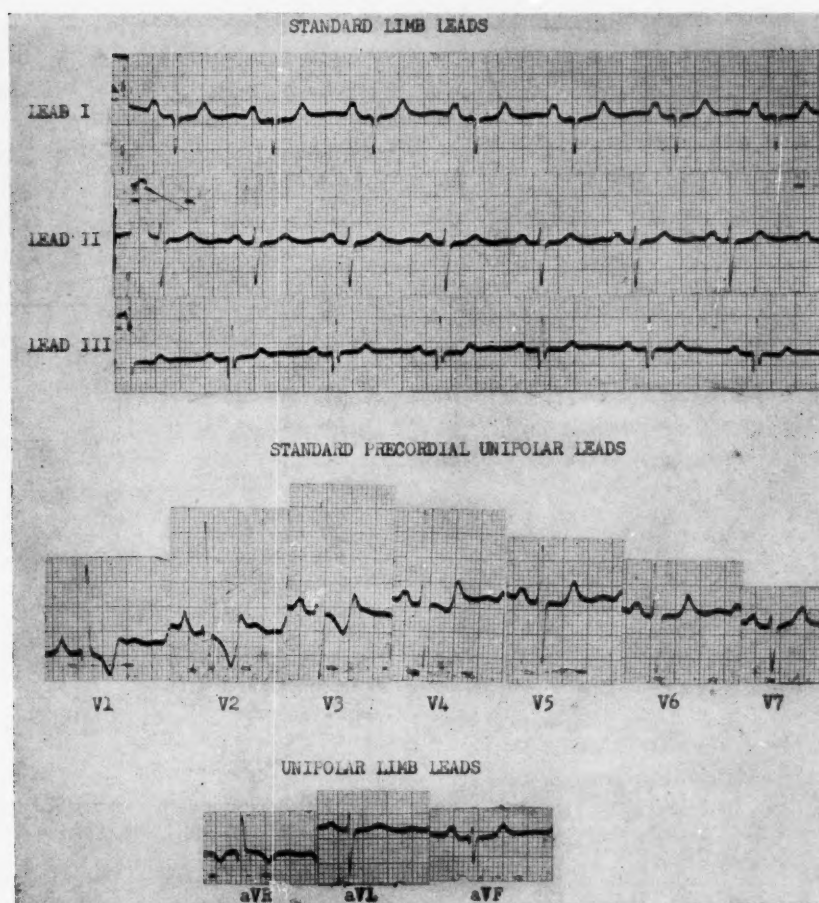


FIG. 2. B, electrocardiogram of Case II showing right ventricular hypertrophy.

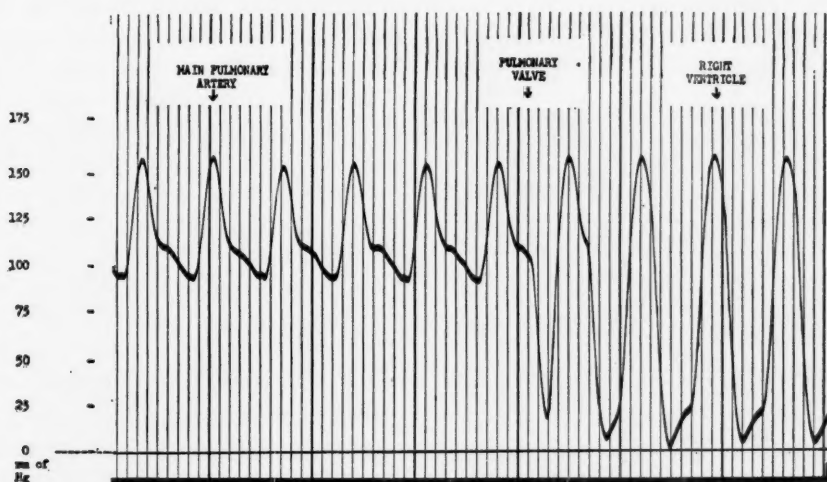


FIG. 2. C, pressure curve during withdrawal of catheter from the main pulmonary artery into the right ventricle in Case II.

defect. The pressure studies in the right ventricle (Fig. 2c) showed systolic hypertension (165 mm. Hg) with normal diastolic pressure (1 mm. Hg). In the pulmonary artery both systolic and diastolic hypertension (165/88 mm. Hg) were present. It is to be noted that pulmonary artery

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pressure was higher than femoral artery pressure. No opportunity was afforded to measure these pressures simultaneously. No evidence of an overriding aorta was obtained.

CASE III. A twenty-three year old white female with a history of heart disease since

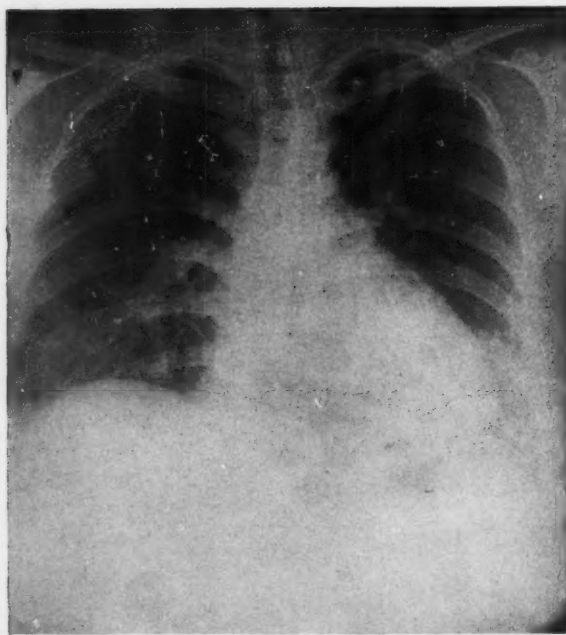


FIG. 3. A, orthodiagram in Case III showing prominent pulmonary arteries.

childhood was admitted for cardiac catheterization. Dyspnea and cyanosis had been noted on exertion. Physical examination revealed an

TABLE II
CARDIAC CATHETERIZATION STUDIES IN TETRALOGY
OF EISENMENGER—CASE II

Station	Pressure (mm. Hg)		Oxygen Content (Volumes Per cent)	Per cent Oxygen Saturation
	Systolic	Diastolic		
Superior vena cava	0	0	16.3	56.2
Right auricle	0	0	17.5	60.6
Body of right ventricle	165	1	17.3	59.6
Conus of right ventricle	165	1	17.3	59.9
Main pulmonary artery	165	88	18.7	64.8
Right pulmonary artery	165	88	19.3	66.7
Peripheral right pulmonary artery	125	80	18.3	63.4
Femoral artery	140	85	21.5	74.4
Coronary sinus	10	0	7.2	24.8

Oxygen capacity: 28.92 volumes per cent

obese white female who was cyanotic. The fingers and toes were clubbed. The blood pressure was 118/92 mm. Hg. The lungs were clear.

Grade I cardiac enlargement was present. The point of maximum impulse was in the fifth intercostal space at the mid-clavicular line. Normal sinus rhythm was present at a rate of 80. P₂ was accentuated. A grade I pulmonary systolic murmur was present.

TABLE III
CARDIAC CATHETERIZATION STUDIES IN TETRALOGY
OF EISENMENGER—CASE III

Station	Average Pressure (mm. Hg)	Oxygen Content (Volumes Per cent)	Per cent Oxygen Saturation
Innominate vein	7	14.8	51.7
Right atrium	11	14.1	49.1
Through interventricular defect	61	23.5	82.0
Right ventricle	65	18.5	66.2
Main pulmonary artery	131	19.2	66.9
Right pulmonary artery	131	17.7	61.7
Peripheral right pulmonary artery	86	17.6	61.1
Femoral artery	21.3	74.1

Oxygen capacity: 28.7 volumes per cent

X-ray of the heart (Fig. 3A) showed prominent pulmonary arteries which at fluoroscopy were noted to have expansile pulsations. In the left oblique there was a moderate right auricular shelf and the right ventricle was grade II enlarged. The electrocardiogram (Fig. 3B) showed right ventricular hypertrophy. The hemoglobin was 21.4 gm. and the red blood count was 7.2 million. The arm-to-tongue circulation time (decholin) was twenty-five seconds, and the arm-to-lung circulation time (ether) was also twenty-five seconds.

Data obtained by cardiac catheterization are summarized in Table III. The oxygen sample obtained when the catheter was passed through the interventricular septal defect into the left ventricle was 23.5 volumes per cent, over 2 volumes per cent more than that in the femoral artery. This indicates a right-to-left shunt from right ventricle to aorta. There is also considerable left-to-right shunt as illustrated by the increase in oxygen from the right auricle to right ventricle and pulmonary artery. The average pressures in the right ventricle and pulmonary artery (Table III) as measured by a saline manometer show the presence of definite hypertension. The discrepancy between the average pulmonary

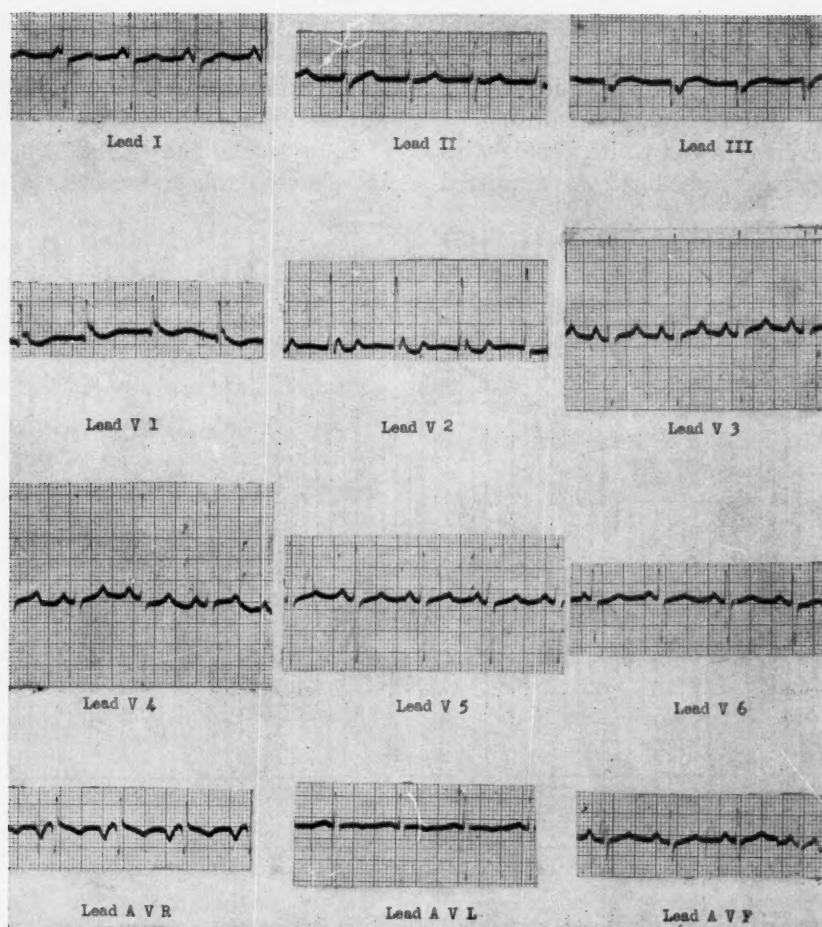


FIG. 3. B, electrocardiogram in Case III showing right ventricular hypertrophy.

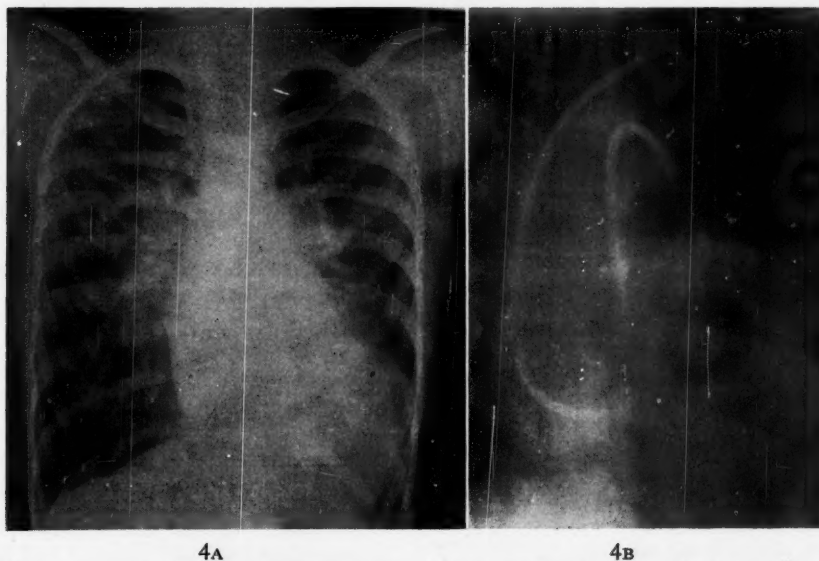


FIG. 4. A, orthodiagram in Case IV showing marked prominence of the pulmonary arteries resulting in "arterial flooding" of the lungs. B, catheter has been passed from the right ventricle into an over-riding aorta (Case IV).

artery pressure (131 mm. Hg) and the right ventricular pressure (65 mm. Hg) was due to the use of saline manometric records which reflect but do not record true diastolic pressures.

CASE IV. A seven year old white female with a heart murmur present since birth was admitted

rhythm was present and the rate was 90 per minute. P_2 was accentuated. There was a grade II systolic murmur loudest at the third left interspace.

X-ray of the heart (Fig. 4A) showed a marked increase in the pulmonary arterial markings.

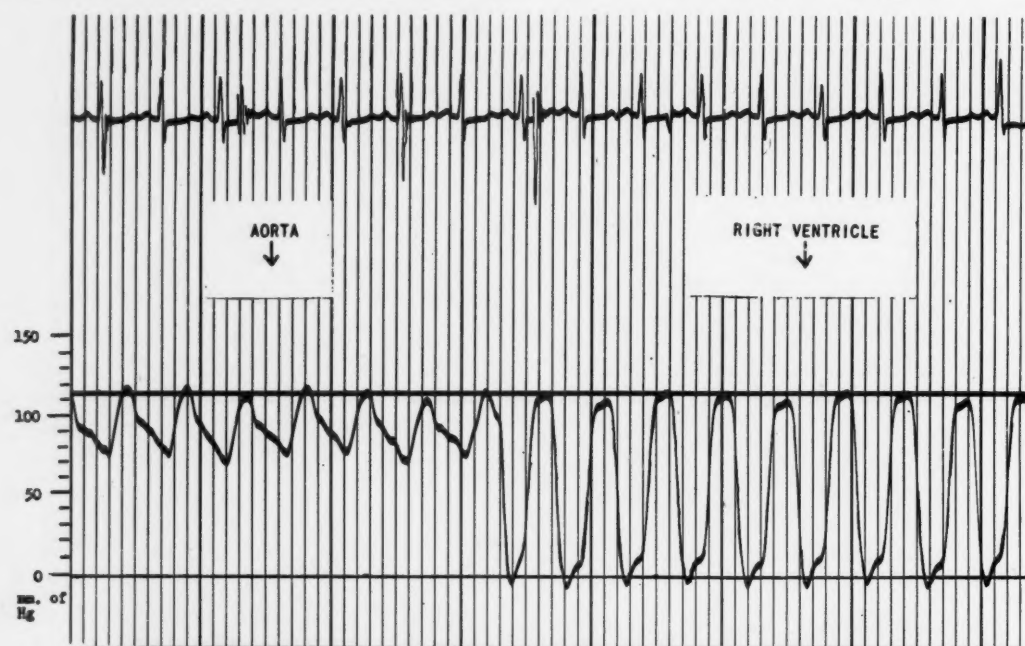


FIG. 4. C, pressure curve during withdrawal of the catheter from aorta into right ventricle in Case IV.

for cardiac catheterization. Physical examination revealed a thin, underdeveloped female child with cyanosis of the nailbeds. There was

TABLE IV
CARDIAC CATHETERIZATION STUDIES IN TETRALOGY
OF EISENMENGER—CASE IV

Station	Pressure (mm. Hg)		Oxygen Content (Vol-umes Per cent)	Per cent Oxygen
	Sys-tolic	Dias-tolic		
Superior vena cava	5	-2	10.8	59.1
Right atrium (high)	5	-2	11.4	62.2
Right atrium (low)	5	-2	8.9	48.6
Right ventricle	120	0	12.0	65.6
Arch of aorta	120	80	14.2	77.6
Descending aorta . . .	120	80	13.8	75.4
Left femoral artery	13.5	74.0

Oxygen capacity: 18.26 volumes per cent

questionable clubbing of the fingernails. The blood pressure was 110/70 mm. Hg. There was grade III cardiac enlargement. Regular sinus

The heart was grade II enlarged. In the left oblique the right ventricle was grade II enlarged. At fluoroscopy marked expansile pulsations of the pulmonary arteries were present. The electrocardiogram showed right ventricular hypertrophy. The hemoglobin was 13.5 gm.

Data obtained by cardiac catheterization are summarized in Table IV. There was an increase in oxygen content from 11.4 volumes per cent high in the right atrium to 12.0 in the right ventricle. This probably represents a left-to-right shunt through an interventricular septal defect. (The oxygen content of 8.9 volumes per cent "low" in right auricle presumably was a sample taken near the coronary sinus.) It was possible to pass the catheter directly from the right ventricle into the aorta. (Fig. 4B.) A continuous pressure record was taken during withdrawal of the catheter from the arch of the aorta into the right ventricle. (Fig. 4C.) The systolic pressure in both aorta and right ventricle was identical (120 mm. Hg). Evidence was thus obtained of overriding of the aorta. Unfortunately the catheter could not be passed into the pulmonary artery.

COMMENTS

Our catheterization findings may now be compared with the criteria for the Eisenmenger complex outlined initially.

With respect to pulmonary hypertension and right ventricular hypertrophy there is ample proof in the four cases presented. The systolic and diastolic pressures in the pulmonary artery were unusually high. The right ventricular systolic pressures corresponded exactly with pulmonary artery systolic pressures, showing the complete absence of pulmonary stenosis. The electrocardiograms gave additional evidence of predominantly right ventricular hypertrophy.

Ventricular septal defect was demonstrated in three patients who showed a rise of oxygen content from the right auricle to right ventricle, or a high ventricular septal defect by a rise of oxygen content from right ventricle to pulmonary artery. In one patient (Case III) the catheter was passed directly through the defect into the left ventricle.

Overriding of the aorta was difficult to demonstrate. In one patient (Case IV) the catheter was passed from the right ventricle into the aorta. In the same patient continuous aortic and right ventricular pressures were recorded. In a second patient (Case I) the brachial artery systolic pressure was exactly equal to pulmonary artery systolic pressure. These pressures although not simultaneously recorded provide indirect evidence strongly suggesting overriding of the aorta. Ideally, in Eisenmenger's complex, equal systolic pressures should be recorded simultaneously in the right ventricle, pulmonary artery and aorta. In the remaining two patients pressure in the pulmonary circuit appeared to exceed that in the systemic circulation. This could be due to increased pulmonary vascular resistance, as mentioned by Bing.⁵

Evidence for overriding of the aorta is also obtainable by analysis of oxygen saturation. For example, if left ventricular blood is entirely saturated, a decreased oxygen saturation in aortic blood could be obtained only

by admixture of right ventricular blood. In fact the relative desaturation may be used as a measure of the degree of overriding. In Case III a sample of left ventricular blood was presumably obtained while in Case IV a sample was taken directly from the aorta. Each showed an increase of oxygen saturation higher than that in the peripheral artery.

Thus with cardiac catheterization overriding of the aorta may be demonstrated in three ways: (1) by passage of the catheter from the right ventricle directly into the aorta, (2) by simultaneous pressure records and (3) by demonstrating admixture of left and right heart blood in the aorta.

SUMMARY

1. Four cases of Eisenmenger's complex are reported and the results of cardiac catheterization are discussed. Right ventricular hypertrophy, pulmonary hypertension, high ventricular septal defect and overriding of the aorta were demonstrated.

2. The practical and theoretic difficulties of demonstrating overriding of the aorta by cardiac catheterization are discussed.

Acknowledgment: We wish to thank Drs. Ray Carter, Patrick Meehan, John Dillon, Harold Miller, Rawley Bledsoe, Tom McAllister, Terry Moran, Howard Roberts, and Austin Wilson, Mr. Paul Munday, Mr. Andrew Farr, Mr. Edward Kirt, Miss Mary Mayo, Miss Grace Gallagher, R.N., and Mrs. R. M. Schmidt, R.N., for their valuable assistance.

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Diagnosis of Masked Hyperthyroidism in Cardiac Patients with Auricular Fibrillation*

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MASKED hyperthyroidism is that form of thyroid disease in which the overactive thyroid gland does not produce classic symptoms but manifests itself by symptoms restricted to a single system. In the older age group the most common type of masked hyperthyroidism is that which presents itself as cardiovascular disease, either as auricular fibrillation, angina pectoris or congestive heart failure. Of these the most common is auricular fibrillation. All patients with auricular fibrillation, particularly if they do not respond to orthodox therapy, should be suspected of hyperthyroidism. This is true even when a definite cardiac etiology is established.

The diagnosis of masked hyperthyroidism must largely depend on laboratory methods since absence of classic clinical symptoms is characteristic of the condition. The standard test for hyperthyroidism, i.e., basal metabolic rate determination, presents certain obvious difficulties. Congestive heart failure, hypertension, orthopnea, pulmonary disease and A-V aneurysm are known to produce elevations of the basal metabolic rate as measured in the standard test. Conversely, the presence of peripheral edema may in some instances reduce the value of the metabolic rate. Finally, patients with masked thyrotoxicosis may not have elevated basal metabolic rates.

While the circulation time is frequently decreased in thyrotoxicosis, this is not reliable diagnostically because it is often affected by heart failure. Reduced circulation time is, however, suggestive of hyper-

thyroidism if anemia, fever and B-hypovitaminosis have been excluded.

Therapeutic trial with Lugol's solution has frequently proved to be of diagnostic value in suspected cases of masked thyrocardiac disease but has the disadvantages of not being definitive and of requiring a relatively long period of observation. In addition, this method postpones the use of therapeutic doses of radioiodine.

Since the work of Hertz and Roberts¹ measurement of the uptake or excretion of radioiodine has become generally accepted as a valuable aid in the diagnosis of thyroid disease. These determinations are not affected by non-thyrogenous cardiac disease or by any other extrathyroid factor which may elevate the basal metabolic rate. Measurement of the plasma protein-bound iodine is another procedure which is accurate and is enjoying increasing popularity. The test with radioiodine, however, is far simpler to perform. The accuracy of radioiodine excretion studies, on the other hand, unfortunately depends upon the completeness of urinary collection as well as the functional integrity of the kidney and therefore low excretions, characteristic of hyperthyroidism, have been confirmed in this study by the more tedious plasma protein-bound iodine determination.

With these newly available methods of study it therefore seemed worth while to investigate a group of patients with auricular fibrillation to search for cases of masked hyperthyroidism.

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MATERIAL AND METHODS

In the cardiac clinics of The Mount Sinai Hospital there were 290 regularly attending patients. Of these forty were found to have auricular fibrillation. Patients with the diagnosis of thyrotoxic heart disease, patients who had received iodine containing compounds such as lipiodol,⁶ and a few patients who were unable to cooperate in the study were excluded. There remained thirty-one patients. An additional twenty-four patients with fibrillation were studied, seventeen from the wards of The Mount Sinai Hospital and seven from the private practice of one of us (S. B. Y.). This makes a total of fifty-five patients investigated.

In each patient a thorough search was made for the etiology of the auricular fibrillation. Routine electrocardiograms, circulation times and cardiac fluoroscopies were obtained. Each patient then received a tracer dose of 100 μ c of I^{131} and the total radioiodine urinary excretion in twenty-four hours was determined using 100 cc. aliquots and a calibrated Geiger-Muller counter. An excretion of less than 20 per cent of the dose with an adequate urinary output is considered to be diagnostic of hyperthyroidism in our laboratory; between 20 per cent and 30 per cent is considered to be suspicious. A value of 30 per cent or more generally excludes the possibility of thyrotoxicosis. Exceptions to these criteria do occur and they are discussed in another paper.² Wherever possible, plasma protein-bound iodine determinations were made in duplicate by a modification of the method of Riggs and Man³ in cases with a low radioiodine excretion. A value greater than 8 μ g per cent is diagnostic of hyperthyroidism.

RESULTS

Of the fifty-five patients who were studied six had radioiodine excretions below 20 per cent. In four of these patients plasma protein-bound iodine determinations were made and were above 8 μ g per cent in three, confirming the diagnosis of hyperthyroidism. In two patients who did not have the benefit

of plasma protein-bound iodine determinations due to technical difficulty, therapy with I^{131} was nevertheless instituted. The therapeutic response was excellent and the diagnosis may be deemed confirmed. In the one patient with a low excretion in whom the plasma protein-bound iodine did not confirm the suspicion of hyperthyroidism it is probable that the low value for radioiodine excretion was due to inadequate urinary output (600 cc. in twenty-four hours).

An additional five patients had radioiodine excretions in the equivocal range (20 to 30 per cent). Of these three were proved to have masked hyperthyroidism by plasma protein-bound iodine determination.

In summary, the diagnosis of masked hyperthyroidism was established in eight of fifty-five patients studied, an incidence of 15 per cent. This is a significant number. However, the series is too small to justify statistical comparison with other reports of the incidence of thyrotoxic heart disease.

COMMENTS

Auricular fibrillation occurs in most types of heart disease. When auricular fibrillation occurs due to thyrotoxicosis, it is of the utmost importance to establish this fact because thyrotoxicosis is curable. Even when thyrotoxicosis is not the sole etiologic agent, its cure may considerably ameliorate the general condition of the patient. Of the thyrotoxic fibrillators, those with overt hyperthyroidism have presented no problem in diagnosis. In those thyrotoxic fibrillators in whom the thyrotoxicosis is manifested solely by auricular fibrillation, the disease is equally crippling and equally curable. The problem is purely diagnostic.

Table I indicates the paucity of significant non-cardiac signs and symptoms suggestive of hyperthyroidism in the eight masked thyrocardiacs uncovered by the technics described. Nervousness was present in seven of the eight cases but this symptom occurred in precisely the same ratio among the non-thyrotoxic fibrillators. Insomnia, dyspnea

and palpitation are not included in the chart because they are common to all cardiac patients who fibrillate.

Prior to this study the auricular fibrillation in these eight cases was considered to be due to rheumatic fever in three, hyper-

cent of cases in the third decade, 31 per cent in the fourth decade, 47 per cent in the fifth decade, 63 per cent in the sixth decade and 83 per cent in the seventh decade. Similarly Ernstene¹³ reports in 1,000 consecutive cases of thyrotoxicosis that auricular fibrilla-

TABLE I
CLINICAL AND LABORATORY DATA IN EIGHT MASKED THYROCARDIAC PATIENTS

Patient	Age	Sex	Basal Metabolic Rates (Per cent)	¹³¹ I Excretion (Per cent)	Plasma Iodine (mg. Per cent)	Weight Loss	Heat Intolerance	Nervousness	Dia-phoresis	Poly-phagia	Tremor	Exophthalmos	Goiter	Fibrillation
S. S.	74	M	*	24	18.5	0	0	+	0	0	+	0	0	8 mo.
O. M.	59	F	-15	18	12.0	0	0	+	0	0	0	0	0	Paroxysmal 2 yr.
M. B.	59	F	†	13	13.3	0	0	+	0	0	+	0	0	Paroxysmal 10 mo.
M. D.	73	M	+16	27	8.8	0	0	+	0	0	0	0	0	17 yr.
S. F.	51	F	+6	12	0	0	0	0	0	0	0	0	2 wk.
M. H.	36	F	+12	8	0	0	+	0	0	0	0	0	4 mo.
S. B.	51	F	‡	23	11.1	+	0	+	0	0	0	0	0	5 mo.
C. G.	68	F	+44	17	12.3	0	0	+	0	0	+	0	0	3 mo.

* Patient left for another hospital where he died of myocardial infarction.

† Unable to take test; amyotrophic lateral sclerosis.

‡ Refused test.

tension in two, arteriosclerosis in two and a combination of hypertension and arteriosclerosis in one. The eight masked thyrocardiacs were of ages ranging from thirty-six to seventy-four, with seven over the age of fifty. In only one patient was the basal metabolic rate found to be higher than 20 per cent (plus 44 per cent). In one patient a low value was recorded (minus 15 per cent); in this instance peripheral edema was present at the time of the test.

Hyperthyroidism has been reported as the etiologic agent in 3.5 to 14 per cent of all cases of auricular fibrillation.⁴⁻⁷ Auricular fibrillation occurs in 5.8 to 34 per cent of all hyperthyroid patients.⁸⁻¹¹ Writers on the subject are in agreement that auricular fibrillation is increasingly common as the age rises. Thus Hamilton¹² reports that in a series of 372 unselected cases of hyperthyroidism auricular fibrillation occurred in no patient under the age of twenty, in 10 per

cent of cases in the third decade, 31 per cent in the fourth decade, 47 per cent in the fifth decade, 63 per cent in the sixth decade and 83 per cent in the seventh decade. Similarly Ernstene¹³ reports in 1,000 consecutive cases of thyrotoxicosis that auricular fibrilla-

tion occurred in 207. Seventy-five per cent of these occurred in patients over the age of forty-five although only 25 per cent of the 1,000 cases were over this age. Thus approximately 150 of the 250 patients over the age of forty-five fibrillated, an incidence of roughly 60 per cent of toxic patients over the age of forty-five with fibrillation. The fact that the average age of our patients was fifty-five may account for the relatively large number of masked thyrocardiacs discovered.

In two of our eight patients the auricular fibrillation was paroxysmal over a period of ten months and two years. In the remaining six auricular fibrillation had been established for from two weeks to seventeen years. The implications of this study are clear. In addition to known thyrocardiacs with auricular fibrillation a significant number of patients with auricular fibrillation due to masked hyperthyroidism may be found

by routine search using radioiodine excretion or plasma protein-bound iodine determination. We believe that one or both of these tests should be made in every case of auricular fibrillation.

SUMMARY

1. Thyrotoxicosis is a frequent cause of auricular fibrillation; conversely, auricular fibrillation is a common manifestation of hyperthyroidism.

2. Fifty-five patients with auricular fibrillation without overt hyperthyroidism were studied by means of radioiodine excretion and plasma protein-bound iodine determination. Eight cases of masked thyrotoxicosis were discovered.

3. The presence of thyrotoxicosis should be excluded in all patients with auricular fibrillation by use of these methods.

Addendum: Since this manuscript was submitted, the seven living patients have been treated with radioiodine in dosage calculated to induce remission of their hyperthyroidism. Six of the seven patients have reverted to normal sinus rhythm. This occurred four to nine weeks after therapy. The seventh patient (M. D.) with long-standing rheumatic heart disease has continued to fibrillate. All of the patients demonstrated subjective and objective improvement in their cardiac status. The high rate of cure of the arrhythmia was not anticipated. How-

ever, we believe, it is not necessarily responsible for the general improvement observed.

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Treatment of Thyroid Carcinoma with Radioactive Iodine (I^{131})*

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THE avidity of carcinomas of the thyroid for radioactive iodine is of considerable therapeutic as well as theoretic importance.¹⁻⁹ The increased uptake of I^{131} in thyroid carcinomas following total thyroidectomy^{9,10} or after the administration of thyrotrophin^{8,9} or of thiouracil^{9,10} has been studied. The efficacy of radioactive iodine in the treatment of thyroid carcinoma and its metastatic lesions has been evaluated, however, in only approximately thirty recorded cases.^{6,7,10-15} The purpose of this paper is to summarize our experience in the study of eleven patients with carcinoma of the thyroid gland, of whom six were treated with I^{131} . The case history of one patient, a fourteen year old boy with carcinoma of the thyroid gland and a solitary pulmonary metastasis, treated with radioactive iodine (I^{131}) has been presented in detail elsewhere.¹⁶ The pulmonary lesion disappeared two months after therapy and in the subsequent year there has been no evidence of recurrence.

Rawson¹⁷ has recently reviewed the use of radioiodine in the study and treatment of thyroid carcinoma. Hamilton, Soley and Eichorn in 1940¹ published the first reports of studies of the function of normal thyroid tissue and thyroid carcinoma utilizing radioactive iodine and autoradiographs. Although two cancers of the thyroid proved incapable of concentrating radioiodine, the investigators noted that "It is possible that

in other cases of carcinoma of the thyroid, radioiodine may be stored in the affected tissue in quantities sufficient for treatment."

In 1942 Keston, Ball, Frantz and Palmer² reported significant uptake and storage of radioactive iodine (I^{130}) in a metastasis to the femur from a malignant adenoma of the thyroid. At necropsy, of many metastatic lesions examined, only one contained significant concentrations of this isotope. Histologically this metastasis resembled differentiated thyroid tissue. Other metastases which were demonstrated histologically to be undifferentiated failed to show uptake. These authors suggested that effective therapeutic internal irradiation might be achieved in well differentiated thyroid tumors and metastases.

Seidlin, Marinelli and Oshry¹¹ in 1946 recorded the successful treatment with I^{130} and I^{131} of a patient with adenocarcinoma of the thyroid removed twenty-one years previously, with subsequent widespread metastases to the lungs, femur, ribs, vertebrae, ilium and skull. The patient presented clinical and laboratory evidence of hyperthyroidism and the metastatic lesions avidly took up radioactive iodine. Subsequent to radioactive iodine therapy definite improvement was reflected by disappearance of pain, increase in weight and the development of hypothyroidism. Roentgenograms "pointed to an arrest if not a regression" of the metastases. Recent papers^{12,13} describe

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the maintenance of improvement in this patient over a period of five years. Seidlin *et al.*¹³ have also reported their evaluation of the effect of radioiodine therapy in twelve patients with carcinoma of the thyroid gland. Three patients were "greatly improved" and five others were classified as "improved." Evidence of destruction of tumor tissue, disappearance of pain and roentgenologic signs of diminution in size or disappearance of metastatic lesions were noted.

Trunnell *et al.*¹⁴ have recently reported the results in nine patients with metastatic carcinoma of the thyroid gland treated with large doses of I^{131} . In four definite improvement was observed as evidenced by decreased tumor size or distinct tumor destruction.

METHODS AND MATERIALS

Eleven patients (seven female), aged fourteen to seventy-four, are the subjects of this report. In each instance the pathologic diagnosis was made from surgically removed specimens. Tracer studies were carried out with 0.5 to 2 millicuries of I^{131} , carrier-free. The urinary I^{131} excretion was measured during the succeeding seventy-two hours. In eight patients (Tables II and III) the amount of I^{131} in the thyroid gland area was quantitated by the four-tube method previously described.^{19,20} To localize extrathyroidal sites of I^{131} uptake the total body surface was surveyed, in each patient, utilizing an end window Geiger-Mueller tube encased in a lead cylinder 20 cm. long, 1.2 cm. thick and 4.6 cm. internal diameter; for sharper localization the end was closed with a lead block having an aperture 2 cm. in diameter. Readings were taken in suspected areas and compared with their opposite anatomic counterparts. Autoradiographs were made by the method of Hamilton, Soley and Eichorn.¹ The tissue content of I^{131} was measured by digesting weighed tissue aliquots in 2N NaOH. After complete digestion aliquots were prepared for beta counting.¹⁸ The basal metabolic rate was measured in duplicate with a Collins Benedict-Roth apparatus, employing the Dubois normal standards as modified by Boothby and Sandiford.²¹ Blood for cholesterol measurements was drawn with minimal stasis after a fast of fourteen hours or more. Measurements of serum

cholesterol were made in duplicate by the method of Myers and Wardell²² using the apparatus for continuous extraction described by Ling.²³ The averages of the duplicate measurements, which checked within 5 per cent, have been reported. Other pertinent clinical and laboratory data are summarized in Tables I to IV.

EVALUATION OF THERAPEUTIC EFFICACY OF I^{131}

During the past year six of the eleven patients with carcinoma of the thyroid gland were treated with therapeutic doses of I^{131} . (Tables I and II.) It is clear that in one of these (Case I, Tables I and II) radioactive iodine achieved a striking result. A metastatic lesion was demonstrated (Fig. 1A) in the right lung of this patient, a fourteen year old boy, one year following a right hemithyroidectomy for papillary adenocarcinoma of the thyroid gland. The uptake of I^{131} in the area of the metastasis following a tracer dose was four times that of an uninvolved control area. Unlike the original case reported by Seidlin, Marinelli and Oshry,¹¹ this patient had no clinical or laboratory evidence of hyperthyroidism. Two months after the administration of the first dose of 78 millicuries of I^{131} the metastatic pulmonary lesion completely disappeared and after subsequent therapeutic or tracer doses of I^{131} localization or concentration of I^{131} in the area of the metastasis was no longer evident. The first therapeutic dose also resulted in complete destruction of functioning thyroid tissue in the neck as evidenced by the development of myxedema, and the absence of I^{131} uptake following its readministration. The destruction of the metastatic lesion concomitantly with the destruction of thyroid tissue in the neck is unusual. Only one of twenty-five patients reported by Trunnell *et al.*¹⁴ showed metastatic tumor tissue which concentrated enough radioactive iodine to justify administering this isotope in therapeutic doses before subjecting the patient to surgical removal of the thyroid. This emphasizes the importance of the tracer study in this patient (Case I) in which evidence of

uptake in the metastasis was demonstrated. At the present time, one year after the first therapeutic dose of I¹³¹ and seven months after the commencement of desiccated thyroid therapy, this patient is entirely well. There are no symptoms of myxedema. His

per cent and the serum cholesterol is 238 mg. per cent per 100 cc. There is no evidence of metastatic recurrence in the neck, lungs (Fig. 1B), long bones, skull or pelvis.

It is more difficult to assess the effect of I¹³¹ in our other patients. In Case II (Tables

TABLE I
DOSE, URINARY EXCRETION, THYROID GLAND RETENTION AND SIDE EFFECTS OF I¹³¹ ADMINISTERED TO SIX PATIENTS WITH CARCINOMA OF THYROID GLAND

Case No.	Date	I ¹³¹ Administered (mc.)	Urine I ¹³¹ Excreted in 72 Hours (Per cent)	Thyroid Gland Uptake in 24 Hours		Side Effects*†			Comment
				(Per cent)	(mc.)	Thyroiditis	Radiation Sickness	Mental Depression	
I	11/20/48	1.7	79	..	.3 (1)	0	0	0	Estimated from urinary excretion Minimal pain, localized tenderness and warmth over the left thyroid lobe, subsided in 4 da. without treatment Anorexia and nausea lasting 24 hr.
	1/8/49	78.0	72	20	15.5	Yes (2)	Yes (3)	0	
	2/18/49	51.0	99	6	3.1	0	0	0	
	4/15/49	8	99	0	0	0	0	0	
	Total	138.7		Total	18.9				
II	8/9/49	20	61 (1)	25	5.0	0	0	0	24-hour urine excretion 2.5% at 48 hr. and 0.5% at 72 hr.
	11/21/49	1	95	7 (2)	0	0	0	
III	2/5/49	70	81	7 (1)	20 (2)	0	0	0	Measured at 96 hr. Estimated from a urinary excretion in 24 hr. of 61%
	4/8/49	17	Not accurate	0	0	0	0	0	
	Total	87		Total	20				
IV	3/10/49	0.5	77	20	0.1	0	0	0	Tenderness below thyroid cartilage, over trachea, 48 hr. after I ¹³¹ ; no palpable mass Anorexia lasting 24 hr. Duration 48 hr. Treated with 8 daily injections of 30 mg. thyrotrophin; I ¹³¹ was administered 48 hr. after last injection Estimated from urinary excretion
	3/15/49	63	87	14	8.8	Mild (1)	Mild (2)	Yes (3)	
	4/12/49	11 (4)	91	..	0.9 (5)	0	0	0	
	5/27/49	33	87	12	4.0	0	0	0	
	Total	107.5		Total	13.8				
V	12/8/48	51.0	79	12	9.5	0	0	0	Estimated from urinary excretion Patient stated he had been taking potassium iodide off and on for the previous 4 wk. Preceded by 6 daily injections of 30 mg. thyrotropic hormone (Armour); I ¹³¹ was administered 48 hr. after last injection
	12/15/48	51	76	6	4.5	0	0	0	
	4/28/49	9 (2)	87	..	1.2 (1)	0	0	0	
	5/9/49	30 (3)	90	0	0	0	0	0	
	5/27/49	33	Not feasible	Not feasible	0	0	0	0	
	6/10/49	35	83	15	5.2	0	0	0	
	Total	209.0		Total	20.4				
VI	11/6/48	8	58	..	3.3 (1)	0	0	0	Estimated from urinary excretion Anorexia lasting 24 hr.
	12/3/48	17	69	..	5.0 (1)	0	0	0	
	12/21/48	41	86	..	5.7 (1)	0	Mild (2)	0	
	1/4/49	3	89	8	.2	0	0	0	
	1/25/49	78	87	..	10.1 (1)	0	0	0	
	Total	147		Total	24.3				

* No toxic effects on the blood or kidney were observed in any case.

† Occurring within first 3 wk. of therapy.

work at school has been of honor caliber. Sexual development has proceeded normally and in recent months sexual maturity has occurred. The basal metabolic rate is -17

I and II) six years after excision and x-ray therapy for a papillary adenocarcinoma of the thyroid gland, regrowth of thyroid tissue was demonstrable on physical examination.

TABLE II
SUMMARY OF DATA IN SIX CASES OF THYROID CARCINOMA TREATED WITH I¹³¹

Case No., Hospital No., Age and Sex	Histologic Diagnosis	Operative Procedure (yr.)	Postoperative X-ray Therapy Tumor Dose (r)	I ¹³¹ Tracer Studies			Time after I ¹³¹ Therapy (mo.)	Clinical Status	Basal Metabolic Rate (Per cent)	Serum Cholesterol mg./100 cc.	Effect of I ¹³¹		Comment	Therapeutic Result
				Urine Excretion in 72 Hours (Per cent)	Thyroid Gland Uptake in 24 Hours (Per cent)	Uptake in Metastases					Local Recurrence	Distant Metastases		
I M-91989 14 M	Papillary adenocarcinoma	Right hemithyroidectomy, 1946	3,850	79	Euthyroid (1)	Yes 4 control area	Before	Euthyroid	+10	300	Right thyroid area (2)	Right mid-lung	Per cent uptake not measured; counts/min. in the euthyroid range ³²	Excellent
							2	Myxedema	-30	614	Not visible by x-ray and no uptake after I ¹³¹	No palpable tissue; marked radioactivity over the right lobe after I ¹³¹	
							4	Myxedema	-30	...	No uptake after I ¹³¹	Not visible by x-ray and no uptake after I ¹³¹	On 60 mg. desiccated thyroid daily for previous 8 mo.; patient completely asymptomatic	
II M-77537 52	Papillary adenocarcinoma	Excision of nodule (right lobe), 1944; inoperable recurrent carcinoma, 1948	4,000 4,000	61 (1)	23	*	Before	Euthyroid	+10	200	Right thyroid area (3)	None	Only first 24 hr. collected	Probable improvement
							4	Myxedema (2)	-14	300	No palpable tissue	None	Started on 60 mg. desiccated thyroid daily, after I ¹³¹ tracer which revealed no gland uptake or selective extrathyroidal uptake	
													Exploration of neck revealed deep-seated, stony-hard, recurrent nodular mass fixed to the trachea and to the large vessels of the neck; inoperable (surgeon's report)	
III M-3406 72 F	Adenocarcinoma	Total thyroidectomy, 1948	None	72	24	*	Before	? Hypothyroid	-10	310	Probable (1)	None	No palpable thyroid tissue; tracer study demonstrated significant I ¹³¹ uptake over thyroid area	Probable improvement
							3	Myxedema	-16	600	No uptake after I ¹³¹	None	On 120 mg. desiccated thyroid daily for previous 7 mo.	
							11	Hypothyroid (2)	Not feasible	255	None		

TABLE II—(Continued)

Before ¹³¹ I Therapy					¹³¹ I Therapy							Therapeutic Result		
Case No., Hospital No., Age and Sex	Histologic Diagnosis	Operative Procedure (yr.)	Postoperative X-ray Therapy Tumor Dose (r)	¹³¹ I Tracer Studies			Time after ¹³¹ I Therapy (mo.)	Clinical Status	Basal Metabolic Rate (Per cent)	Serum Cholesterol mg./ 100 cc.	Effect of ¹³¹ I		Comment	
				Urine Excretion in 72 Hours (Per cent)	Thyroid Gland Uptake ¹⁸ in 24 Hours (Per cent)	Uptake in Metas- tases					Local Recurrence			Distant Metastases
iv M-71621 52 M	Papillary adenocarci- noma	Total thyroid- ectomy, 1943; excision of local recur- rence, 1947	4,000 (1943) 2,400 (1947) 3,000 (1949)	77	20	None	Before	Hypothyroid	-23	505	Firm, fixed mass (approx. 30 mm.) in right thyroid area No change No change	Mediastinum No change No change	On 180 mg. desiccated thyroid daily for previous 4 mo.	No improvement
v M-3144 66 M	Undiffer- entiated carcinoma	Biopsy, 1948	8,000 (1)	92	..	*	Before	Euthyroid	+7	350	None	Marked diminution in size of subterminal extension of pri- mary tumor after x-ray therapy	No improvement
							5	Myxedema	-18	...	Yes (2)	None	Fungating mass growing in fistulous tract over left thy- roid lobe area; no ¹³¹ I up- take; total excision of mass; histologic diagnosis: undif- ferentiated thyroid carcinoma	No improvement
							11	Hypothyroid	Not feasible	None	Died October, 1949; post- mortem examination not ob- tained	No improvement
vi M-2923 61 F	Undiffer- entiated carci- noma	Total thyroid- ectomy, 1943	Yes (dose not known)	58	Euthy- roid (1)	None	Before	? Hypothyroid	-20	275	Right thyroid area No change (2)	Skull, middle ear, brain stem No change	Per cent uptake not measured; counts/min. in the euthyroid range ²² At autopsy, 5 mo. after ¹³¹ I therapy, no normal thyroid tissue was found in neck; on microscopic examination small areas of necrotic tumor tissue present	No improvement

* No metastases demonstrated.

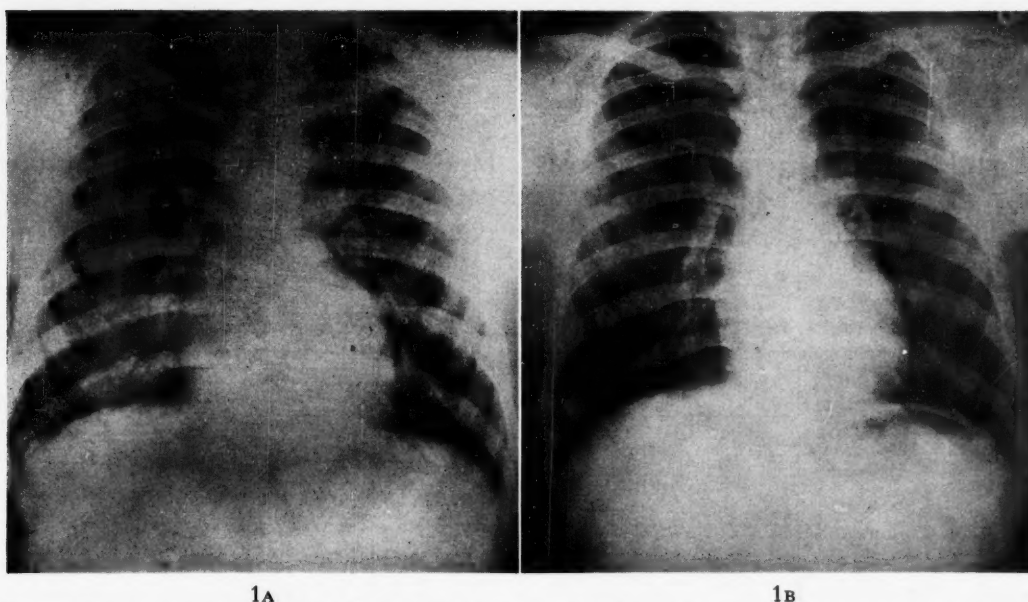


FIG. 1. Chest roentgenograms of Case I (M91989). A, taken December 27, 1948, two years postoperatively and before I¹³¹ therapy; the lesion in the right mid-lung field measures 1.5 cm. in diameter. B, taken February 3, 1950, thirteen months after the first therapeutic dose of I¹³¹; the lung fields are clear.

At re-exploration Dr. David D. Berlin considered the case inoperable because of the presence of deep-seated, stony-hard, recurrent nodular masses firmly fixed to the trachea and to the large vessels of the neck. A diagnosis of recurrent carcinoma was made. Biopsy was not feasible because of marked friability, excessive bleeding and attachment of the tumor tissue to the surrounding structure. The tracer studies one year later showed a 23 per cent uptake (euthyroid) in the thyroid gland region after twenty-four hours. Following the therapeutic dose of I¹³¹ there was a 25 per cent uptake after twenty-four hours. (Tables I and II.) Disappearance of the palpable nodular tissue followed I¹³¹ and myxedema occurred ten weeks after the therapeutic dose. Although it is too early to assess the final effect of I¹³¹ in this patient, four months after the therapeutic dose there is no palpable tissue in the neck and following a tracer dose no evidence of uptake in the neck region was demonstrated. The therapeutic procedure in this patient has therefore been considered to be worthwhile.

In Case III (Table II) total thyroidectomy for adenocarcinoma had been performed in

December, 1948. Tracer studies two months later (Table II) showed an uptake in the thyroid gland region within normal limits although no thyroid tissue was palpable in the neck. Following the administration of 70 millicuries of I¹³¹ destruction of remaining functional thyroid tissue was apparently accomplished inasmuch as myxedema occurred and no uptake in the thyroid gland region could be demonstrated after repeated tracer studies. Eleven months after the therapeutic administration of I¹³¹ (Table I) there has been no evidence of regrowth of tissue in the thyroid gland region. The procedure therefore has been considered to be worthwhile in this patient.

No apparent improvement following I¹³¹ and the induction of myxedema were observed in Cases IV, V and VI (Tables I and II); metastatic lesions present before I¹³¹ therapy in Cases IV and VI were demonstrable after I¹³¹ and in Case V progression of a local recurrence occurred after I¹³¹. In Case VI at autopsy five months after the therapeutic induction of myxedema no thyroid tissue was found in the neck. There was marked extension and involvement by metastases of the brain stem, skull and

middle ear. A few areas of scattered necrotic tumor tissue were found in the region of the thyroid gland.

Following I¹³¹ tracer studies the remaining five patients were treated with total thyroidectomy (Cases VII and X)^{10,28} or with hemithyroidectomy (Cases VIII, IX and XI).

demonstrated the uptake of I¹³¹ in the follicular and alveolar portions of papillary adenocarcinoma. They were unable to demonstrate uptake in tumors that were predominantly papillary. Contrariwise, carcinoma of the anaplastic type did not concentrate I¹³¹.

TABLE III
SUMMARY OF DATA IN FIVE CASES OF THYROID CARCINOMA NOT TREATED WITH I¹³¹

Case No., Hospital No., Age and Sex	Histologic Diagnosis	Operative Procedure	Preoperative I ¹³¹ Tracer Studies			Tissue Studies		Comment
			Urine Excretion in 72 hr. (Per cent)	Thyroid Gland Uptake in 24 hr. ¹⁹ (Per cent)	Uptake in Metastases	I ¹³¹ Content ²²	Radioautography	
VII M-3902 35 F	Diffuse adenocarcinoma (1)	Total thyroidectomy	50	Increased (2)	None	Previous excision of thyroid nodule (scirrhous carcinoma) in 1933 Per cent uptake not measured; counts/min. in range observed in patients with hyperthyroidism, but patient clinically euthyroid
VIII M-7792 67 M	Papillary adenocarcinoma	Hemithyroidectomy	27 (1)	36	None	11% (2)	No uptake in tumor tissue	Collection incomplete Radioactivity in the entire surgical specimen (weight 120 gm.) was measured by the four-tube method
IX 51 F	Adenocarcinoma	Hemithyroidectomy	Not feasible	36	None (1)	No uptake in tumor tissue	Paraplegia, probably due to spinal cord metastases; no evidence of I ¹³¹ uptake
X M-4671 59 F	Adenocarcinoma	Total thyroidectomy	54	28 (1)	None	Normal thyroid 6 x carcinoma tissue	No uptake in tumor tissue	Following thyroidectomy an I ¹³¹ tracer study revealed an 8% uptake in the thyroid gland region in 24 hr.; 2% in 96 hr.
XI M-329 69 F	Papillary adenocarcinoma	Exploration and removal of large nodule	Not feasible	Euthyroid (1)	None	Normal thyroid 300 x carcinoma tissue	Per cent uptake not increased; counts/min. in euthyroid range Expired 5 hr. after operation

RELATIONSHIP OF I¹³¹ UPTAKE TO HISTOLOGIC DIAGNOSIS

The exact nature of the metastatic lesion in Case I is not known; the location and size of the lesion precluded biopsy. The pathologic report on the surgically removed right lobe of the thyroid gland was papillary adenocarcinoma, and the pathologist noted that the tumor appeared to be of low grade malignancy. The age of the patient and clinical course are consistent with these observations. The increased avidity of the metastatic lesion for I¹³¹ is consistent with the view that the tumor was differentiated.^{2,4,5,7,8,24-27} Fitzgerald and Foote²⁷

In four other patients (Cases VIII, IX, X and XI) I¹³¹ distribution studies or autoradiographs showed no evidence of increased uptake or localization of I¹³¹ in the turnover tissue. (Tables III and IV.) The pathologic diagnosis in two instances (Cases VIII and IX) was papillary adenocarcinoma and in the other two (Cases X and XI), adenocarcinoma. It is of interest that in each instance the twenty-four-hour thyroid gland uptake after a tracer dose as measured by external counting was in the euthyroid range. (Table III.)

Case VII (Table III) is of particular interest in that a high uptake was demonstrated by

external counting. Although autoradiographs and I¹³¹ tissue studies were not feasible, the histologic picture of diffuse adenocarcinoma with only a few minute areas of involutinal thyroid tissue suggests that the high uptake was at least in part attributable to the avidity of the tumor for radioactive iodine.

DEVELOPMENT OF MYXEDEMA FOLLOWING I¹³¹

Seidlin *et al.*²⁸ and Rawson *et al.*¹⁰ recommend thyroidectomy prior to I¹³¹ therapy in instances of thyroid carcinoma with metastasis. In two of our patients (Cases II and V) (Table II) surgical exploration of the neck was carried out and total thyroidectomy considered unfeasible. In three patients (Cases VII, IV and VI) (Table II) total thyroidectomy had been accomplished two months to five years previously. In each instance I¹³¹ tracer study had shown uptakes in the thyroid gland region in the euthyroid range. (Table II.)

Accordingly, in each of the six cases the induction of myxedema was accomplished with I¹³¹. One to six therapeutic doses of radioactive iodine were administered to each patient. (Table I.) The total number of millicuries administered to each patient was 21 to 209, the average 118 millicuries. The retention in the thyroid gland area was 5 to 24 millicuries.

In three patients (Cases I, II, and III) (Table II) clinical and laboratory evidence of myxedema appeared after the first dose of 20 to 78 millicuries of I¹³¹; the retention in the thyroid gland area was 5 to 20 millicuries. In the other three cases the exact relationship of the development of myxedema to a particular therapeutic dose could not be determined.

The time interval (Table II) and the dosage range (Table I) for the development of myxedema were similar to observations in euthyroid cardiac patients treated with myxedema-inducing doses of I¹³¹.^{29,30} In each instance (Table II) after the development of myxedema the uptake in the thyroid gland region and the urinary excretion were

in the range observed in euthyroid cardiac patients with I¹³¹-induced myxedema.^{29,30} The administration of additional doses in each patient was for the purpose of detecting uptake in metastatic lesions or recurrent tissue in the thyroid region.

TABLE IV
RADIOACTIVITY (I¹³¹) MEASUREMENTS IN CASE XI TWO DAYS
AFTER AN ORAL DOSE OF 1.7 MILLICURIES

Sample	Counts/ min./gm. Tissue	Per cent Thyroid Counts per Gram Tissue *
Normal thyroid.....	48,150	100
Metastatic carcinoma of thyroid to:		
Lung.....	149	.32
Rib.....	127	.27
Vertebra.....	114	.24
Peribronchial lymph node...	87	.18
Skull.....	42	.10
Tissue free of carcinoma:		
Lung.....	248	.51
Uterus.....	119	.25
Kidney.....	97	.20
Ovary.....	92	.19
Spleen.....	76	.16
Liver.....	76	.16
Adrenal.....	40	.10
Muscle.....	40	.10
Pituitary.....	0	0

* Counts/min./gm. normal thyroid tissue was taken to equal 100 per cent.

CLINICAL MANAGEMENT OF I¹³¹-INDUCED MYXEDEMA

Seidlin *et al.*^{4,9,13,18,27} and Rawson *et al.*^{10,14} observed that increased uptake in metastatic lesions followed the development of myxedema and/or the administration of thyrotrophic hormone or thiourea derivatives in some patients. Accordingly, we have allowed complete myxedema to develop and persist for at least three months before administering thyroid. A longer period was not considered practical because of the severe discomfort associated with myxedema. No evidence was obtained during this period (Cases IV, V and VI) of increased uptake in metastatic lesions; in two of these patients (Cases IV and V) thy-

rotrophin* was also administered without increased uptake. (Table I.) In one patient (Case v) increased growth of a locally recurrent tumor mass was apparent during the period of myxedema.⁹

After these tracer studies had been completed the administration of desiccated thyroid, 60 to 180 mg. daily, was begun with prompt relief of the symptoms of myxedema.

ADVERSE EFFECTS OF I^{131}

Adverse reactions were mild and required no specific therapy. They consisted of mild radiation sickness (Cases I, IV and VI) and thyroiditis (Cases I, III and V). (Table I.) We have not observed clinical or laboratory evidence of hyperthyroidism in these patients. However, Trunnell¹⁴ observed three instances of temporary hyperthyroidism following the administration of large doses of radioactive iodine, and we have noted this phenomenon in euthyroid cardiac patients treated with radioactive iodine.^{29,30} Trunnell also recently described¹⁴ the occurrence of one instance of fatal pancytopenia following the administration of an accumulated dose of 638 millicuries of I^{131} . Other blood changes observed by these authors included transient lymphopenia and a small decrease in hemoglobin; in five of nine patients in whom bone marrow studies were made a decrease in total cell count with a reversal of the erythroid myeloid ratio was observed. Examinations of the blood and urine in our patients revealed no significant immediate or delayed changes following I^{131} in Cases I, II, V and VI. (Tables I and V.) In Case IV a significant drop in hemoglobin and red count was observed six months after I^{131} . It is unlikely that the blood changes observed in this patient were due to myxedema³¹ since thyroid has been administered and the basal metabolic rate was normal. A small decrease in hemoglobin and red count has been observed in two other patients (Cases III and VI). It is

* We are indebted to Dr. John R. Mote of Armour Laboratories, Chicago, Ill., for the thyrotrophin used in these studies.

of some interest that in one patient (Case II) polycythemia vera had been present for many years and four months after the induction of myxedema by radioactive iodine no change in the blood picture has been observed. The absence of serious blood complications in our patients is presumably related to the smaller doses of I^{131} used as compared to those used by Trunnell.

Considerable attention has been given to the question of untoward effects of I^{131} on the gonads. Distribution studies in our laboratories³² and those of Rall et al.³³ are consistent with the view that no selective concentration of I^{131} occurs in the gonads. The occurrence of normal sexual development in Case I of our series suggest the absence of adverse effects of I^{131} on the gonads.

SUMMARY

1. Eleven cases of carcinoma of the thyroid gland have been studied. Evaluation of the therapeutic efficacy of radioactive iodine (I^{131}) in six cases is presented. In one patient with papillary adenocarcinoma of the thyroid gland and a solitary metastasis to the lung resolution of the pulmonary metastasis followed treatment with radioactive iodine, I^{131} . The therapeutic effects of radioactive iodine have been considered to be worthwhile in two other cases while in the remaining three cases no improvement was noted.

2. Following I^{131} tracer studies total thyroidectomy was carried out in two of the remaining five cases and hemithyroidectomy in three cases. I^{131} distribution studies or autoradiographs showed no evidence of increased uptake or localization of I^{131} in the tumor tissue. Therapeutic doses of I^{131} therefore were not administered.

3. Myxedema was induced in each of the six patients treated with radioactive iodine by one or more doses. In two patients thyroidectomy was attempted but was not feasible. In three others total thyroidectomy apparently had been accomplished previously. In each instance tracer studies showed uptakes in the thyroid gland region in the

euthyroid range. The total dose in each patient ranged from 20 to 209 millicuries; the retention in the thyroid gland was 5 to 24 millicuries.

4. No serious adverse effects of I¹³¹ have been observed. Transient thyroiditis and radiation sickness occurred in three of six patients after therapeutic doses. In one patient six months after 108 millicuries of I¹³¹ a significant decrease in hemoglobin and red blood count was found.

5. Radioactive iodine is an important therapeutic agent in the treatment of selected instances of thyroid carcinoma.

Addendum: Since the paper was submitted the patients in Cases II and IV of Table I have expired. The cause of death in June, 1950, in Case II eight months after I¹³¹, was extensive hepatic vein thrombosis; the clinical picture was consistent with Chiari's syndrome and the patient was known to have had polycythemia vera. At autopsy no thyroid tissue could be seen grossly; the tissue found in the thyroid area consisted of four almond-shaped calcific nodules and microscopic examination showed, in addition to marked fibrosis and calcification, involution of a parenchyma which consisted of tumor tissue. The tissue was less anaplastic than the original tumor, did not contain mitoses or show invasion of the capsule or vessels; no metastases were found. It would therefore appear that the surgeon's opinion that there had been recurrence of thyroid tumor was correct and that this mass had been considerably reduced by radioactive iodine therapy.

The patient in Case IV expired in March, 1950, ten months after the last dose of I¹³¹. Autopsy showed widespread metastases from the thyroid carcinoma. It is of interest that certain of the metastases showed an extraordinarily increased avidity for radioactive iodine.

Case I has now been followed an additional ten months, making a total follow-up of approximately two years and has remained perfectly well without evidence of recurrence of the pulmonary lesion or evidence of tumor elsewhere.

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Management of Carcinoma of the Prostate*

Study of Hormonal and Surgical Therapy in 100 Patients

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THE purpose of this communication is to describe a plan of management of carcinoma of the prostate which uses both biologic and surgical measures known now to be effective in the control of the disease. The endeavor has been made to use radical surgery early, to diminish by orchidectomy the androgenic stimulus and to utilize the inhibitory effect of estrogens simultaneously in all cases since 1946. With these considerations in mind a critical study of 100 consecutive patients with carcinoma of the prostate admitted to the Peter Bent Brigham Hospital from 1946 to 1949 was made. This survey illustrates various problems of treatment and management as well as describing the early results of different types of therapy. Careful examination of the prostate of men over fifty years of age is necessary in order that early asymptomatic carcinoma may be discovered. More frequent exploration of these will lead to more cures by complete removal of the prostate; other cases with regional extension of carcinoma may undergo enough regression with hormonal therapy to become operable and be completely extirpated as shown by Colston,¹ Guitterez² and others. Much can be done for widespread carcinoma of the prostate by judicious use of hormonal and radiation therapy; palliative surgery is often effective for relief of obstructive symptoms.

ANALYSIS OF 100 CONSECUTIVE CASES OF CARCINOMA OF THE PROSTATE

Table I shows the age distribution of this group of 100 patients treated in the Peter

Bent Brigham Hospital for carcinoma of the prostate during the four-year period, 1946 to 1949. Only ten of these patients were below the age of sixty. The great majority, 77 per cent, were men between sixty and

TABLE I
AGE DISTRIBUTION

Age	No.
Under 50	1
50-60	9
60-70	42
70-80	35
80-90	13
Total	100

eighty years, the number being evenly divided between these two decades. Thirteen patients were men over eighty years of age, the oldest being ninety; in fifteen of these 100 patients the diagnosis was originally made and treatment started prior to 1946, but all were subsequently admitted during this four-year period for further treatment and are therefore included in this series. Two of these fifteen were operated upon for benign hyperplasia of the prostate nine to thirteen years ago, a small focus of carcinoma being discovered in the surgical specimen of each at that time; in neither case was a secondary total prostatectomy performed and both were seen between 1946 to 1949 with clinical evidence of carcinoma. Ten of the 100 patients were formerly operated upon for benign prostatic hyperplasia. Eight of these ten had suprapubic prostatectomy and carcinoma appeared later, the time interval varying between ten months and twenty-five years.

* From the Surgical Service and Tumor Clinic of the Peter Bent Brigham Hospital and the Department of Surgery, Harvard Medical School, Boston, Mass. This study was assisted by the American Cancer Society, Massachusetts Division.

In one instance the neoplasm was found seven years after a perineal prostatectomy and another appeared four and a half years after a transurethral resection. The diagnosis of carcinoma was proved by pathologic examination in five of these eight and by

of the prostate and bladder underwent successful total cystectomy and prostatectomy.

The 100 cases were divided into three groups of clinical stages as shown in Table III. The first group includes all patients who had lesions which by palpation were con-

TABLE II
DIAGNOSIS OF CARCINOMA OF PROSTATE

	No.
Suspected on entry.....	60
Incidental finding on physical examination.....	30
Surgical pathologic examination.....	10

clinical evidence supported by an elevated serum acid phosphatase and roentgenographic evidence of bony metastasis in the remaining three.

From Table II it is seen that carcinoma of the prostate was suspected in only 60 per cent of the patients at the time of admission to the hospital. All of these sixty patients sought treatment because of urinary difficulty and carcinoma was discovered by rectal palpation in each case. Further information was gained from acid phosphatase and roentgenographic studies to confirm the diagnosis.

It is interesting that neoplasm of the prostate was an incidental finding on physical examination of thirty patients admitted primarily for an unrelated complaint. Eight of the latter proved to be operable with total prostatectomy. Ten of the 100 cases were discovered only on pathologic examination of the surgical specimen, the presence of carcinoma being unsuspected either at the time of examination or of operation. These specimens of so-called carcinoma *in situ* or occult carcinoma showed only small areas of neoplasm within the hyperplastic gland. Such a finding logically should raise the question of a secondary total prostatectomy as well as institution of endocrine therapy at once. One of these ten unsuspected lesions was found in a man aged fifty-four who had total cystectomy for carcinoma of the bladder, a small focus of carcinoma being found in the prostate gland on pathologic examination. One other patient aged eighty-one having known cancer

TABLE III
CLINICAL STAGE ON ENTRY

Localized	
Recognized clinically.....	16
Not recognized.....	10
Regional metastasis.....	45
Remote metastasis.....	29
Total.....	100

finer within the capsule of the prostate gland and without evidence of regional or remote metastases. Of the twenty-six patients in this group sixteen were recognized clinically as having carcinoma; the evidence consisted of a hard nodule or induration within the prostate without extension into the seminal vesicles or laterally and, therefore, presumably were operable. Ten of the twenty-six cases were not recognized clinically but were found only on pathologic study of the operative specimen as mentioned earlier. Apparently nothing was felt at the time of the operation which was indicative of cancer in these ten patients. The second group represents all cases in which there was evidence on palpation of extension of the carcinoma into the seminal vesicles, floor of the bladder or laterally into the soft tissues about the rectum. There were forty-five in this group. Many of these had other evidence of extensive involvement such as anemia, debility, pain, elevated acid phosphatase and abdominal masses. The third group consists of all patients who had roentgenographic evidence of bony metastasis, a total of twenty-nine cases. The commonest site of demonstrable metastasis was the pelvis, with the spine, femurs, ribs, other long bones, skull and lungs being involved with diminishing frequency.

The serum acid phosphatase determination aids in the diagnosis of carcinoma of the prostate and also provides a biologic test of activity of the carcinoma after treatment has been instituted.^{3,4} Acid phos-

phatase is normally produced by the epithelial cells of the adult male prostate, but it is also present at the site of osseous or other metastasis secondary to carcinoma of the prostate.⁵ The serum acid phosphatase level rises when the extent of osseous and

TABLE IV
CORRELATION OF ACID PHOSPHATASE AND CLINICAL STAGE
AT ENTRY

	No.	Local- ized	Re- gional	Meta- static (To Skele- ton)
Below 5.0 Gutman units	54	17	25	12
Above 5.0 Gutman units	32	2	13	17
Not taken before treat- ment.....	14	7	7	..

Total.....	100	26	45	29

soft tissue involvement is sufficient to allow large amounts of the enzyme to pass into the blood stream. However, the metastatic tissue in some patients may not produce enough acid phosphatase to cause significant elevation, the cells of such lesions often showing marked anaplasia. The range of the normal acid phosphatase value varies from one laboratory to another, and the test must be done under careful conditions. Hemolysis of red blood cells with release of their acid phosphatase into the serum will cause a slight elevation of the acid phosphatase normally present in the serum. The use of formalin in conjunction with the test destroys all acid phosphatase liberated by the hemolyzed red cells but does not affect the prostatic acid phosphatase, making the results easier to interpret.⁶ For the purpose of this study and to minimize false positive errors a level of 5.0 Gutman units per 100 cc. was arbitrarily selected as definitely elevated.

Table IV correlates the acid phosphatase determinations with the clinical stage of the lesion at the time treatment was instituted. There were fifty-four patients who had an acid phosphatase below 5.0 Gutman units, the level arbitrarily selected as definitely

elevated. Thirty-two patients had determinations above 5.0 Gutman units and in fourteen instances the test was not utilized before therapy was instituted. In nineteen patients with a localized lesion in the prostate seventeen had an acid phosphatase below 5.0 Gutman units while two were above this value. One of these had an acute prostatitis a short time before which may influence this determination. Of thirty-eight patients with regional involvement by carcinoma twenty-five had an acid phosphatase below 5.0 Gutman units, however, thirteen patients had readings above this value. In most instances this last group of thirteen had extensive soft tissue involvement with no roentgenographic evidence of skeletal metastases. In the third group with demonstrable bony metastasis twelve patients had an acid phosphatase below 5.0 Gutman units while seventeen were definitely elevated. A few patients in this latter group were given estrogens prior to the laboratory test which rapidly reduces an elevated serum acid phosphatase in approximately 70 per cent of cases.

The pathologic diagnosis of carcinoma of the prostate was proved in sixty-two of the 100 patients, five by perineal biopsy, forty-eight by operative specimen and nine by autopsy. The diagnosis was ascertained in sixteen additional patients by clinical findings and roentgenographic evidence of bony metastasis and in eight other patients by clinical findings plus an elevated serum acid phosphatase. In only sixteen of the 100 patients was the final diagnosis made on the basis of palpation alone.

The management of carcinoma of the prostate was determined by such factors as the clinical stage of the disease, age and general condition of the patient, the presence or absence of obstruction of the bladder and finally what the patient would consent to.⁷ The last factor is often a deterrent to adequate therapy because patients refused orchidectomy or failed to continue estrogenic therapy postoperatively. Table V shows the type of initial therapy instituted and the clinical stage of the disease at the

time. Nineteen of the 100 patients were considered operable and had total prostatectomy. Five of these had estrogens for a varying length of time before operation (thirty to sixty days), with regression locally of the process in each case. Of the total

total prostatectomy because of the discovery of adenocarcinoma in what was thought to be a benign prostate recently removed by the suprapubic route at another hospital. Total prostatectomy and orchitectomy were carried out one month after the previous

TABLE V

Initial Therapy	No.	Not Recognized	Local	Re- gional	Re- mote	Cas- tra- tion	Estro- gen	No Hormonal Treatment
Total prostatectomy	19	1	10	8	..	13	12	4
Simple prostatectomy	29	9	2	12	6	17	22	4
Orchidectomy and estrogens only	34	..	1	16*	17†	34	34	..
Orchidectomy only	5	..	1	2	2	5
Estrogens only	8	..	2	5	1	..	8	..
No treatment	5	2	3	5
	100	10	16	45	29	69	76	13

* Includes four who had perineal biopsy

† Includes one who had perineal biopsy

prostatectomies ten had local involvement only, the carcinoma being confined within the prostate; eight had extension into the region of the seminal vesicles. The one patient with unrecognized carcinoma in this group had a total cystectomy for carcinoma of the bladder; the prostate was found to contain a small focus of carcinoma. In this group of nineteen radical prostatectomies thirteen were treated also with orchidectomy, x-ray castration in one instance, and nine of these received estrogens simultaneously. Two were given estrogens without orchidectomy and four had no antiandrogenic treatment. It should be mentioned that when orchidectomy was not performed it was because the patient refused except in five instances in which the patient was seriously ill from some other disease which contraindicated any surgery.

It is interesting to note that only eleven of these nineteen patients who had total prostatectomy were hospitalized for primary urinary symptoms. Of the remainder seven patients were found to have a nodular area in the prostate on a yearly physical examination or when admitted for an unassociated complaint. One patient was referred for

operation. He is well and without evidence of metastasis thirty months later.

The pathologic extent varied considerably in this group of nineteen patients. A small local focus of carcinoma without lymphatic involvement was found in eight instances. Another eight patients showed extension of the process into the lymphatics or perineural lymphatics and four of these had direct extension into the base of the seminal vesicles. The remaining three showed extension either into the urethra at the apex of the prostate or about the base of the bladder. One eighty-one year old patient had both papillary carcinoma of the bladder and carcinoma of the prostate with extension into the seminal vesicles. He is well one year after ureteral transplantation to the sigmoid and total cystectomy with prostatoseminal vesiculectomy and removal of iliac glands. A high index of suspicion regarding cancer of the prostate must be developed by the physician in examining men over the age of fifty if cures are to replace palliation. The disease must be discovered long before symptoms develop in order to effect a cure.

The presenting symptom in the group of twenty-nine patients who had simple prosta-

tectomy was either prostatism or total urinary retention in all cases. Nine patients were not suspected of having carcinoma preoperatively, the clinical findings being those of diffuse hyperplasia of the prostate, and even at operation carcinoma was not suspected in seven instances. Two of the twenty-nine patients had clinical evidence of localized carcinoma. One was ninety years of age and the obstruction was treated with a transurethral resection of the prostate. He continues to be well one year later taking estrogens and without evidence of metastases. The other patient who had a localized prostatic nodule considered clinically to be carcinoma was reported to have benign hyperplasia on frozen section biopsy and underwent only a simple perineal prostatectomy. This we regard as an error in clinical management for if the clinical diagnosis is made, then the radical operation should be performed or nothing done until permanent sections have been made of the biopsied material. Permanent sections later showed the presence of adenocarcinoma. Twelve of this group of twenty-nine patients had regional involvement by the carcinoma and six showed roentgen evidence of bony metastasis.

The type of operation performed to relieve obstruction in these twenty-nine cases was chosen to fit the needs of the individual patient as far as possible.⁷ Fourteen patients underwent transurethral resection of the prostate as a palliative measure, four resections being done in men who had earlier prostatic surgery for obstruction due to carcinoma but later developed sufficient recurrence at the bladder outlet to require a resection. One of these fourteen patients who went into acute retention after a subtotal gastrectomy had a resection for what was thought to be benign hyperplasia and pathologic examination revealed the presence of adenocarcinoma.

Ten patients of the twenty-nine had a perineal exploration and simple enucleative prostatectomy. In six instances the perineal approach was used in order to evaluate the extent of carcinoma, hoping to do a total

prostatectomy; however, extension beyond the region of operability prevented this. In four patients carcinoma was unsuspected preoperatively. One of these was found to have inoperable carcinoma on exploration and an enucleation of the obstructing lobes was then done. The three others had small foci of carcinoma found only on pathologic examination of the specimen. Three patients of the twenty-nine cases had a suprapubic prostatectomy, two having unsuspected carcinoma revealed on pathologic examination. Two patients underwent retropubic prostatectomy for benign enlargement of the gland and a focus of adenocarcinoma was found in the operative specimen.

Within this group of twenty-nine patients seventeen had orchidectomy, all but one being done at the time of original admission for carcinoma of the prostate. Eight of these seventeen were treated with estrogens simultaneously, and six others were given estrogens shortly before their demise after having had orchidectomy for a variable period before. Eight of the twenty-nine cases were treated only with estrogens, two receiving estrogens four and twelve years after the original microscopic diagnosis was made. Four patients of the twenty-nine failed to return after operation and received no antiandrogenic therapy until recently when reexamination disclosed evidence of diffuse spread of the disease.

From Table v it is seen that thirty-four patients were treated at entry with only orchidectomy and estrogens. Sixteen patients had regional involvement by carcinoma and seventeen had bony metastasis. The one patient in this group with a localized prostatic carcinoma was a man of seventy-eight who had previously had a partial cystectomy for papillary carcinoma of the dome of the bladder. Five patients in this group had perineal exploration and biopsy to prove the diagnosis of carcinoma.

Five patients had orchidectomy only for treatment. Only one of these had localized involvement and this was in a patient five years after a transurethral resection for

benign hyperplasia; he refused further prostatic surgery. Eight patients were treated only with estrogens, the reason being that they were considered too poor risks to undergo any surgery and had other primary complaints. Five patients had no treatment for carcinoma of the prostate; two died of cardiovascular disease, one of carcinoma of the pharynx and a fourth died of a pathologic fracture of the spine from carcinoma of the prostate shortly after entry. The fifth patient was admitted three years ago because of hematuria and was found to have bony metastasis from carcinoma of the prostate. He refused all treatment but is asymptomatic and working daily at the time of this report. This is indeed an example of the variable behavior of cancer which confounds the evaluation of different methods of treatment.

RESULTS

We are able to obtain very recent data concerning ninety-eight of the 100 patients within three months of the date of this report. The remaining two patients were known to be alive within the past seven months.

As seen from Table VI sixty-two patients are living and thirty-eight are dead. Twenty-nine patients died of carcinoma of the prostate, and nine died of other causes. Fifty-one patients were treated with both orchidectomy and estrogens and thirty-four (66 per cent) are living an average of twenty-four months after treatment was instituted. Eighteen patients were treated with orchidectomy only although six of this group had estrogens as well shortly before their demise. Seven (39 per cent) of these have survived an average of thirty-three months after treatment was instituted. This result does not, however, detract from the value of orchidectomy when used in combination with estrogenic therapy and/or radical surgery. It does illustrate the inadequacy of this therapy when used alone. Eighteen patients were treated solely with estrogens, thirteen (72 per cent) are still alive an average of twenty-two months after treatment

was instituted. Thirteen patients received no antiandrogenic therapy and eight are still alive an average of thirty-three months after the diagnosis of carcinoma of the prostate was made; four of these had total prostatectomy and are living without any clinical sign of carcinoma at present; four had palliative prostatectomy and show extension of the disease. The results in this group would undoubtedly have been improved in morbidity and longevity if not in ultimate mortality by initial orchidectomy and continual or intermittent estrogenic therapy.

The results for nineteen patients who had total prostatectomy have been very encouraging; sixteen are still alive, but three of these have shown spread of the disease since operation. The thirteen who are free from evidence of neoplasm are now an average of twenty-six months since operation. The type of hormonal therapy utilized along with total prostatectomy is shown in Table VI. The three patients who died all had orchidectomy and estrogens although this therapy was withheld in one case until bony metastasis developed four years after operation. It should be mentioned that two of the three who died showed perineural lymphatic involvement at the time of operation and two showed involvement of the seminal vesicles as well. The three patients who had a recurrence are interesting in several respects. One had total prostatectomy in 1941 showing only local involvement of the prostate pathologically. In 1949 he returned with painful bony metastases and orchidectomy and estrogens were promptly instituted. Roentgen therapy has been necessary for relief of pain subsequently. Another patient had a total prostatectomy in 1942 and the specimen showed perineural lymphatic involvement. In 1944 bony metastases were demonstrated and orchidectomy was performed and estrogenic treatment started. The metastases disappeared six months later, and he is completely free of symptoms or any evidence of carcinoma at present. The third had a total prostatectomy in 1936, but it was believed

that some carcinomatous tissue was left behind at the apex of the prostate. Radon and x-ray therapy were also used and subsequent resection was necessary to preserve the patency of the urethra. Nevertheless, he is alive today and free of demonstrable cancer

COMMENTS

The management of carcinoma of the prostate is based on a careful clinical evaluation of each individual patient. Treatment is then directed toward eradication of the process in all operable cases by total prosta-

TABLE VI

	No.	Total Prosta-tectomy	Simple Prosta-tectomy	Living	Dead (Carcinoma Prostate)	Dead (Other Causes)
Orchidectomy and estrogens.....	51	9	8	34 (66%) (24 mo.)	14	3
Orchidectomy.....	18	4	9*	7 (39%) (33 mo.)	10*	1
Estrogens.....	18	2	8	13 (72%) (22 mo.)	3	2
No antiandrogenic therapy.....	13	4	4	8 (67%) (33 mo.)	2	3
Totals.....	100	19 (16 living)	29* (14 living)	62	29 38 dead	9

* Six had estrogens prior to death.

but with considerable scarring about the vesical neck causing urinary incontinence.

Of the twenty-nine patients who had simple prostatectomy only fifteen still survive. It is noteworthy that all but one of these survivors either had unrecognized carcinoma originally or were considered to have only regional involvement at the time of operation. In fact, three of the patients who had simple prostatectomy for what was believed to be benign hyperplasia but proved to have small foci of carcinoma in the surgical specimen are now three and a half, four and thirteen years postoperative. Two of these three now show extensive regional involvement and were started on antiandrogenic therapy, and the third did not return for examination but reported that he was entirely well. Excluding these three special cases the eleven other survivors are now living an average of fifteen months since simple prostatectomy. The type of antiandrogenic therapy used along with simple prostatectomy is pointed out in Table VI. All nine of those who had orchidectomy without estrogens are now dead, three of the eight who had estrogens without orchidectomy are dead and one in each of the other two groups.

tectomy, diminution of the androgenic stimulus by orchidectomy, use of the inhibitory effect of estrogens, palliative relief of obstruction by transurethral resection when necessary and provision for relief of pain by other means as indicated.

Experience has shown that cure of carcinoma of the prostate can be obtained by total prostatectomy if the lesion is confined to the gland and these patients must be continually sought.⁸⁻¹⁴ In the last decade, owing to the work of Huggins, the response of carcinoma of the prostate to castration and estrogenic therapy has produced new concepts of management.^{4,15,16} Cases once considered inoperable are now being treated after hormonal therapy by total prostatectomy with encouraging results although not enough time has elapsed for final evaluation. It has been our conviction that hormonal therapy consisting of both orchidectomy and estrogens should be instituted at once in all cases of proven carcinoma whether the lesion is operable or not. This policy has been followed for four years whenever possible. The excellent statistical survey of Nesbit and Baum¹⁷ indicates that the combination of the two forms of therapy provides a definite survival advantage over

either castration or estrogen alone and that the former is more effective than the latter when each is used alone. Carcinoma of the prostate has a widely variable rate of growth governed by various known and unknown factors, and the response to anti-androgenic therapy is often dramatic and long lasting, but is not uniform and is subject to relapses.¹⁸ The biologic behavior of this lesion seems to be related to the age of the patient but the susceptibility to hormonal treatment has not yet been correlated with the different histologic types of prostatic carcinoma with sufficient consistency to prognosticate response to hormonal therapy on the basis of histology.¹⁹ The pathways of metastatic spread are locally via lymphatics and remotely via the venous circulation. The lymphatics may be regarded as a resistant pathway of spread, the pelvic glands acting in the capacity of temporary barriers, progression through which is slow. Invasion of the blood stream, owing to the lack of such barriers, results in remote metastases in bones and parenchymatous organs. Furthermore, the alteration of metastasis to treatment shows a variable response depending on the tissues involved. A consideration of these factors and the experience gained from treating the 100 cases described have resulted in the following approach to management based primarily on the clinical stage of the process.

Small Indurated Prostatic Nodule Suspected of Being Carcinoma. From the work of Moore,²⁰ Rich,²¹ and Kahler²² it is known that 75 per cent of all carcinomas of the prostate arise in the atrophied posterior lobe known as the surgical capsule of the prostate. Here they are readily palpable and in their earliest stages are felt as small, irregular, indurated areas lying anywhere on the posterior surface of the prostate. As invasion of the lateral lobes occurs the prostate becomes stony hard, and with extension of the carcinoma outside of the prostate palpable fixation is found. An indurated area within the prostate in a man over fifty years of age should be suspected of being carcinoma. The degree and extent of the induration can be determined better by palpating the

prostate at the time of cystoscopy, the pressure of the instrument aiding in determining mobility and size of the lesion. A roentgenogram of the pelvis will rule out prostatic calculi as the cause of nodules within the prostate as well as often demonstrate metastasis if present, but at this stage visible metastasis or elevation of the acid phosphatase is seldom demonstrated. Biopsy of the bone marrow should be done in all such patients having anemia (hemoglobin 12 gm. per cent or less).²³ One of the most difficult points in diagnosis is the differentiation of irregular fibrotic areas of chronic inflammation and at times acute inflammation from carcinoma. A history of urinary tract infection along with other signs of infection are important evidence and the patient can be checked at intervals to note any change in the indurated area of the gland.

The most certain method of establishing the diagnosis when carcinoma is suspected is that of open perineal biopsy, selecting the most indurated area for section. Frozen section biopsies are reliable if positive, but frequently great difficulty may be encountered in the interpretation of the material. If carcinoma is proven on frozen section, total prostatectomy can be done forthwith. A negative frozen section report should be regarded as not final and one must then proceed according to the circumstances and evidence at hand. If exploration of the prostate increases the likelihood of carcinoma as determined by palpation and the character and appearance of the gland, total prostatectomy should be done. When permanent sections prove the presence of carcinoma, then orchidectomy and estrogenic treatment should be instituted. If one is in doubt, then it is wiser to await the results of permanent sections before proceeding with radical surgery. The reason for carrying out these antiandrogenic measures is the real possibility that the tumor has already silently spread beyond the gland as illustrated in the studies of Alyea and Rundles.²³ If the likelihood of carcinoma decreases on exploration and biopsy of the prostate, further surgery can be deferred until the permanent section report is avail-

able and then, if positive, total prostatectomy and orchidectomy done a few days later. Occasionally occult carcinoma of the prostate is discovered on pathologic examination of the prostatic tissue removed by transurethral resection or other type of prostatectomy for what was believed to be benign hyperplasia. Total prostatectomy should be considered always under these circumstances.²⁴

The surgical technic used in total prostatectomy is a modification of that developed by Dr. Hugh Young²⁵ with removal of not only all the prostate but also a cuff of adjacent bladder neck and both seminal vesicles. Great care is used in repairing the anterior portion of the bladder neck and in making a snug anastomosis of the posterior portion to the uninjured membranous urethra; by using this technic incontinence has become an infrequent problem. Only one of the nineteen patients having total prostatectomy had total incontinence while another had slight stress leakage of urine.

Hard Nodule Characteristic of Carcinoma and Limited to the Prostate. Certain patients will present hard nodules confined locally in one or both lobes of the prostate which leaves little or no doubt in the examiner's mind regarding the diagnosis of carcinoma. In some there may be also slight induration at the base of the adjoining seminal vesicle. These are candidates for perineal exploration and total prostatectomy. Preoperatively and while arrangements for operation are being made, they should be given estrogens for about one month which will cause softening usually if carcinoma is present and also regression of induration in the region of the seminal vesicle. Total prostatectomy is then done under more optimal conditions for cure. Orchidectomy should be done once the presence of carcinoma is proven and estrogens continued postoperatively. Three patients not included in this series were thought by palpation to have carcinoma with regional extension. Estrogens were started on each and orchidectomy was performed on two who had elevation of the acid phosphatase to 6.2 and 4.5, respectively. After two to three

months total prostatectomy was carried out in each case after a striking local regression had occurred. In each of these specimens no evidence of carcinoma was found but marked squamous metaplasia and chronic inflammation was found in each instance. Preoperative biopsy had not been attempted because there was no doubt regarding the clinical diagnosis. The response to hormonal therapy was impressive but we are left without an established diagnosis of carcinoma in each of these cases.

Regional Involvement by Carcinoma of the Prostate. Carcinoma of the prostate spreads by direct extension into adjacent connective tissue, the seminal vesicles, base of the bladder and posteriorly around the rectovesical fascia to surround the rectum. The degree and extent of this local spread usually can be determined fairly well by careful rectal palpation and cystoscopy, noting particularly the fixation of the prostate to the surrounding structures, the gripping of the instrument by the posterior urethra and the deformity of the vesical neck and base.

The treatment offering the most to these patients in the way of survival, comfort and avoidance of later complications is bilateral orchidectomy and continued use of estrogens. Orchidectomy diminishes the source of androgens necessary for tumor growth and estrogen counteracts the remaining androgens from the adrenals as well as possibly directly or indirectly inhibiting the growth of the prostatic carcinoma by some other mechanism. It may be desirable to secure a biopsy of the lesion at the time of the orchidectomy to identify and to determine the degree of differentiation of the tumor. This can be done most satisfactorily by perineal exposure of the prostate although needle biopsy through the perineum may be occasionally quite satisfactory. In patients with urinary obstruction usually enough shrinkage of the prostate occurs within two to three weeks to allow satisfactory voiding. Some of these patients may need palliative surgery for the relief of obstruction,²⁶ satisfactorily accomplished in many cases by a transurethral resection

of the prostate and only rarely permanent drainage by catheter is necessary. Regression of the primary lesion occasionally occurs to the point that there is no longer any palpable evidence of neoplasm outside the prostatic capsule and exploration seems indicated.

Metastatic Carcinoma of the Prostate. Perineural lymphatic involvement by carcinoma occurs early in the course of the disease at first invading the lymphatics within the prostatic capsule²⁷ and probably also the capillary circulation of the blood stream. It is believed that metastasis develops by each of these pathways spreading to the lymphatics of the periprostatic and pelvic nerves and via venous channels to the bony pelvis and spine which may then be involved by direct invasion of the marrow spaces through the ostia. Likewise, the usual pelvic lymphatic channels are permeated, with gradual spread to the iliac and aortic glands and the entire lymphatic system. This pathway is probably not important in determining bony metastasis, however. The other course of metastasis is by way of the blood stream, tumor emboli entering the vertebral veins and by retrograde flow subsequently to give rise to pelvic, spine and skull lesions.^{28,34}

Definite evidence of metastatic carcinoma is obtained through roentgenographic studies of the bones, chiefly the spine, pelvis, femurs and ribs. Occasionally parenchymal lesions of the lungs are demonstrable, but this is usually a late manifestation of the disease. An elevated serum acid phosphatase is indicative of metastatic carcinoma of the prostate with rare exceptions. A recent extensive infarction of the prostate may give a transiently high serum acid phosphatase.³¹ Several other diseases may cause slight elevation of the serum acid phosphatase chiefly among which are hyperparathyroidism, severe Paget's disease and extensive osseous metastasis secondary to carcinoma elsewhere in the body, usually the breast. These latter usually cause elevation of the alkaline phosphatase indicating osteolytic activity which occurs in carcinoma of the prostate only in advanced stages of the disease.

A normal acid phosphatase, on the other hand, does not rule out the presence of metastasis as the metastatic tissue in some patients may not produce enough acid phosphatase to cause significant amounts to be detected in the serum. Presumptive evidence of metastatic carcinoma in the absence of demonstrable bony metastasis or elevated acid phosphatase is the relief of pain and improvement of anemia with antiandrogenic therapy. This relief usually occurs shortly after treatment has been instituted.

Treatment of metastatic carcinoma consists of orchidectomy, the continued use of estrogens and such general supportive measures as are indicated. The dosage of estrogen varies with the clinical response of the patient. A dose of ethinylestradiol in doses of 0.05 mg. or stilbesterol of 1 mg. twice daily has furnished satisfactory control in most cases; this can be increased gradually provided the patient has no unfavorable reactions to the drug in those cases not showing a satisfactory response.

Reactivated Metastatic Lesions. Following orchidectomy and estrogenic therapy there is symptomatic and objective improvement in 70 per cent of cases of extensive carcinoma of the prostate. This symptomatic improvement occurs rapidly, pain due to pressure on nerves is relieved, frequency due to obstruction of the urinary passages is relieved, the appetite improves, anemia is corrected and there is a gain in weight and strength. There is usually a corresponding decrease in elevated serum acid phosphatase values to normal levels in three to six weeks. In the majority of instances the prostate softens and usually loses most of the characteristics of carcinoma except for its abnormal fixation to surrounding structures.

This symptomatic and objective improvement may continue over a long period of time. Sooner or later, however, there may be a return of symptoms, new or increased osseous metastasis may be demonstrable, or a rise in acid phosphatase may occur in a considerable number of cases in spite of continued estrogenic therapy. This delayed reactivation of the disease is one

of its most interesting features. Often the primary tumor remains soft and small while there is obvious distant spread of the process. Autopsy examination at this stage may show very little carcinomatous tissue in the prostate itself in contrast to the metastatic lesions or in comparison with the previous biopsies of the prostate before treatment was begun. In other instances, metastases may remain quiescent while the local lesion gradually enlarges and extends.

Besides a return of symptoms of pain or urinary obstruction either a rise in acid phosphatase or increased bony metastasis demonstrable roentgenographically may be manifest in these cases of delayed reactivation although one or both of these may show no change. This reactivation occurs in spite of continued estrogenic therapy. Although it is thought by some that the tumor has lost its sensitivity to estrogens, as demonstrated in heterologous transplants of prostatic carcinoma,²¹ it is also possible that increased androgen secretion of the adrenal may be an important factor. Further investigation of treatment directed at this possibility is being carried out.

Treatment of relapses after a sustained period of improvement consists of drastic increases in the amount of estrogens administered daily, the dose being adjusted upwards until improvement occurs. Failure of such increases to cause improvement is not uncommon. Painful bony metastasis can be treated with adequate doses of x-ray therapy over proper sites with resulting marked improvement and relief of pain for weeks and even months. Urinary obstruction at this time seldom occurs because of shrinkage of the primary tumor by previous therapy. Other measures which have been tried are irradiation or removal of both adrenals in an attempt to reduce the extragonadal source of androgens,^{32*} irradiation of the pituitary to reduce its stimulating

effect on the adrenal and possibly directly on the tumor,³³ and the use of progesterone to block the pituitary. Various forms of chemotherapy, e.g., the folic acid derivatives and antagonists, urethane and nitrogen mustard have given hope in isolated cases for an eventual discovery of an anticarcinogen that is non-toxic to the normal cell. These methods are yet experimental and temporary improvement in some cases follows but considerable side effects from the treatment itself as well as psychologic factors and spontaneous regression of neoplasm make results difficult to evaluate.

SUMMARY

A study of 100 consecutive patients with carcinoma of the prostate treated during the four-year period 1946 to 1949 and a short term follow-up of all cases is presented. Radical prostatectomy was performed in nineteen patients and only simple prostatectomy could be done in twenty-nine, hormonal treatment alone was administered to forty-seven and five patients received no treatment. The basis of biologic management was the elimination of the androgenic stimulus of the testicles and the employment of the antiandrogenic influence of estrogens. The indication for biopsy of suspected carcinoma, for total prostatectomy in operable lesions and for the use of other measures in the control of the disease are discussed.

CONCLUSIONS

1. The results in the treatment of carcinoma of the prostate can be improved by earlier discovery of the disease if followed by radical prostatectomy and institution of hormonal therapy.

2. The most effective hormonal treatment consists of orchidectomy combined with estrogenic therapy. This should be used in all cases when practicable, including those having radical prostatectomy because of the possibility of antecedent unrecognized metastatic spread either local or remote.

* A study of the 17-ketosteroid excretion before and repeatedly after orchidectomy is being made in order to determine the optimum dose of estrogenic therapy, since it is entirely possible that excessively large doses of estrogen may stimulate adrenal androgenic secretion. The use of cortisone in small doses is being studied in an attempt to reduce further adrenal androgen secretion.

3. When carcinoma of the prostate is regional in extent, preliminary hormonal therapy is usually effective in causing local regression. Often the lesion will diminish in size sufficiently to permit operative removal which is indicated in selected cases.

4. The earliest possible institution of all known effective measures is indicated in the treatment of carcinoma of the prostate.

5. The management of the reactivated local and metastatic lesion continues to be a major problem demanding further investigation of pituitary-adrenal factors as well as chemotherapy.

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Effects of Certain Antispasmodic Drugs on the Intact Human Colon, with Special Reference to Banthine (β -Diethylaminoethyl Xanthene-9-Carboxylate Methobromide)*

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DISTURBANCES in motor function of the gastrointestinal tract are among the most common disorders encountered by physicians. In the pathogenesis of the irritable colon syndrome (mucous colitis) sustained hypermotility of the colon has been widely regarded as an important factor. The administration of so-called "antispasmodic" drugs has long played a major role in its therapy; but although many such agents, alone and in combination, have been employed, none has proven consistently satisfactory.

As pointed out by Posey and his associates⁹ it is hardly surprising that these agents are disappointing when one considers the manner by which they are usually evaluated. The methods most commonly used are *in vitro* and *in vivo* studies with animal intestine. Activity of isolated animal intestine is inhibited by most of the antispasmodic preparations now in use. In intact animals parenteral injections of these agents will usually block the effect of stimuli such as acetylcholine and barium chloride. With this as a background the clinician then administers the drug orally to patients in an attempt to evaluate its effect upon inconstant symptoms. The fallacies of this latter type of study are so obvious that they do not require elaboration.

The hiatus between pharmacologic testing and the clinical trial of antispasmodics

has been bridged by only a few investigators^{4,6,9} who recorded human intestinal motility before and after the oral administration of a drug. The most extensive study was that of Posey et al.⁹ who examined the action of nine supposedly antispasmodic drugs, including many agents in common use, on the human small and large intestine. None of them had a significant depressing action upon the gastrointestinal tract.

In this type of study it is desirable that certain principles be observed. *First*, it is important that intact human subjects be employed. It is probable that a segment of bowel proximal to a stoma does not serve the same physiologic purpose as that segment does in the non-operated human. This statement is based largely upon observations of the pattern of emptying of ileostomies and colostomies. Often this is in striking contrast with the known motor function of these segments of bowel in the intact individual. *Second*, it is probably essential that one study areas of intestine that are known to have particular physiologic significance. *Third*, the desirability of testing the agent on a large number of subjects is clear. If only a few individuals are examined, well known biologic variations in response could lead to an erroneous conclusion.

The term "antispasmodic" is used here to refer to a drug which inhibits contrac-

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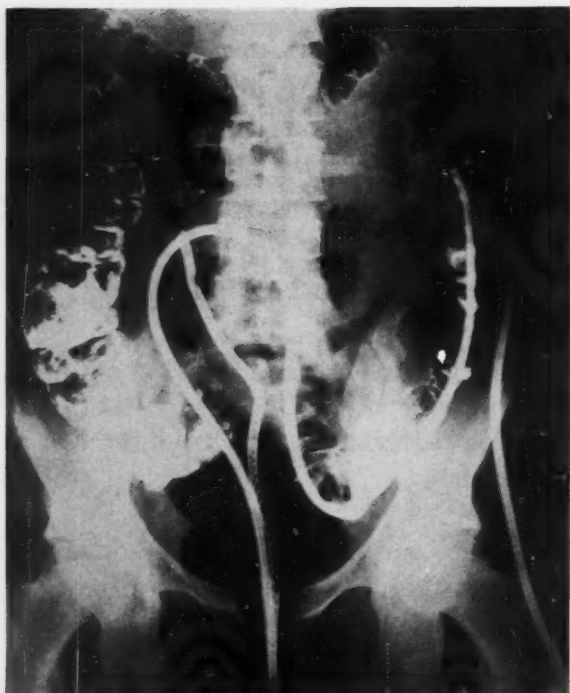


FIG. 1. Roentgenogram of a patient with two balloons in the colon, one in the sigmoid and one at the splenic flexure. These were inserted by the method described.

tions of the gastrointestinal tract, regardless of its mode of action or its specific effect on the various types of intestinal motor activity. The requirements of a satisfactory drug can easily be defined. If the agent is not effective upon oral administration, it can be of little routine clinical use. The preparation must have significant action on the intestinal tract in a dosage range which is not toxic or incapacitating. It should not have cumulative effects which would preclude its use for a period of months. Its action should be sustained for several hours. By these standards none of the antispasmodic agents evaluated by Posey can be considered satisfactory.

The purpose of this report is to describe results obtained with a simple technic for evaluation of antispasmodic drugs in man, with particular reference to a new compound, banthine. Previous studies in this laboratory have shown the relevance of physiologic changes in the sigmoid to the genesis of the irritable colon syndrome.^{2,3} For this reason, as well as the ease with which the sigmoid may be studied in intact

man, we have focused our attention upon examination of the effects of several pharmacologic and physiologic agents upon the sigmoid colon.

METHOD OF STUDY

Continuous kymographic recordings have been made of the wave-like movements of the human sigmoid and descending colon. The subjects have been, for the most part, patients in good general health from the medical wards and the outpatient department of our hospital. None has had evidence of organic disease of the colon. All have been prepared for the experiments by one or more enemas of physiologic saline and by omission of the preceding meal, thus providing a fasting period of either six or sixteen hours preceding the experiment.

Our method of intubation of the distal colon is modified after the technic of Adler, Atkinson and Ivy.¹ A single distensible balloon, 10 cm. in length, is cut from condom rubber and is attached to the end of a red rubber stomach tube (No. 16 Fr.), which in turn is stiffened internally by a coiled steel spring extending to its tip. The balloon and tube are lubricated with jelly and are introduced through the proctoscope and threaded upward through the distal colon by means of alligator forceps. After this the proctoscope is removed and the tube is taped to the skin near the anus. The balloon may thus be placed, in most instances, anywhere between the splenic flexure and the rectosigmoid junction. (Fig. 1.) Its position is verified by fluoroscopy.

For the remainder of the procedure the patient lies supine upon a hospital bed, and is cautioned to avoid coughing, sneezing, laughing and raising the head or the legs. The tube is connected to a large glass U-tube which serves as a water manometer and which bears an ink-writing pen on a float of balsa wood, usually coated at the bottom with paraffin wax. Through a T-tube the system is filled with air from a syringe; 50 to 75 cc. usually suffice to produce a baseline pressure of 6 to 8 cm. of water, as measured directly on the tracing. With this degree of filling the tension of the balloon is not a factor; when inflated to this degree outside the body the pressure reading is zero. Reduction of the baseline pressure to 4 cm. or elevation to 14 cm. seldom produces any significant change in the form of the tracing. Only a few subjects feel the initial distention of the balloon as a dull lower

abdominal ache; after a few minutes there are no continuing sensations attributable to the apparatus itself. In experiments on healthy subjects the balloon has rarely been displaced downward and has never been passed out of the rectum. The subjects are not conscious of a desire to defecate except in rare instances when the balloon enters the rectum. The experiments have been limited in time almost entirely by hunger, restlessness and desire to urinate.

Tracings are recorded at a kymograph speed of 1 cm. per minute. In over 300 observations on control periods of one to three hours' duration the pattern of the tracing has been a nearly continuous succession of irregular and complex waves, with changes in the baseline rarely exceeding 2 cm., and with interruptions of wave-like activity seldom longer than five minutes at a time. The recorded waves vary greatly in amplitude and frequency in different subjects. (Fig. 2.) In the same individual, however, and in the same experimental period, they show little change after the first twenty minutes. Type I and II contractions, as defined by Templeton and Lawson¹⁰ and Adler, Atkinson and Ivy¹ are discernible in the usual wave-patterns whereas sustained tonus changes (type III contractions) are less frequently seen. Coughing, sneezing or any other action which produces tension in the muscles of the abdominal wall causes sharp but usually transient upward movements of the recording pen. These "spikes" are easily distinguishable with practice from true colonic contractions. When any doubt has existed as to the nature of these artifacts, the subject has been constantly observed and if doubt still remained the results have been discarded.

In most of our experiments a single recording balloon has been used. It is not difficult to pass two balloons to different levels of the left colon but the wave patterns recorded by the two balloons are nearly always qualitatively, and usually quantitatively, similar. In such experiments with tandem balloons most contractions have been recorded simultaneously in the two tracings. This further supports the conclusion of Adler, Atkinson and Ivy⁶ that the majority of wave-like contractions in the distal colon are non-propulsive.

In studying the effect of drugs upon sigmoid motility, a suitable control tracing of thirty to sixty minutes is obtained. The agent is then administered and the study continued for approximately two hours longer. In approximately half

of the experiments to be reported the blood pressure and pulse rate were recorded at five-minute intervals throughout the procedure.

Drugs tested in this manner were atropine, syntropan, trasentine and banthine. Banthine (beta-diethylaminoethyl xanthene-9-carboxy-

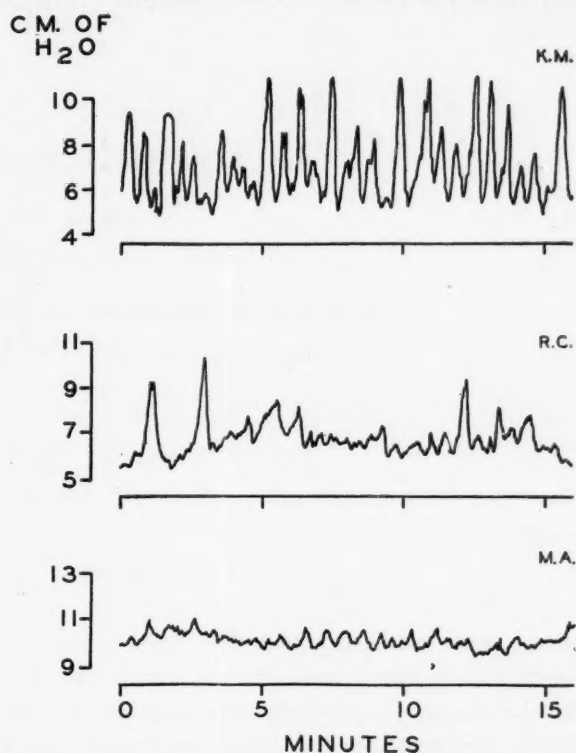


FIG. 2. These normal sigmoid tracings are representative of those obtained in resting individuals without organic disease of the colon.

late methobromide)* is a new quaternary ammonium salt which has been found by Longino, Grimson and their associates⁸ to be effective in blocking post-ganglionic parasympathetic nerve endings. These parasympatholytic or "atropine-like" effects were prominent in the dosage range tested in man; there was almost no indication of synaptic block. In animals autonomic ganglia can be blocked by amounts of banthine four to eight times that necessary for the parasympatholytic effect; when still larger doses are used in animals, curariform effects are noted.⁷ This agent is effective by oral as well as parenteral administration. Longino and Grimson⁸ reported that it is well tolerated by man over long periods of time.

RESULTS

Atropine sulfate has been administered orally to five subjects. One of them received

* Supplied by Dr. I. C. Winter, G. D. Searle & Co.

0.4 mg. and one 0.6 mg. without any effect upon sigmoid motility. Two subjects were given 1.0 mg. (Fig. 3) and the other was given 0.9 mg. In each of these there was only a slight decrease in sigmoid motility which persisted for fifteen to sixty minutes. Atro-

diminishes total motility of the descending colon of man by 23 to 52 per cent. Their subjects were four patients with sigmoid colostomies. Posey et al.⁹ reported a temporary (eight to twenty-seven minute) inhibition of colonic activity in each of four

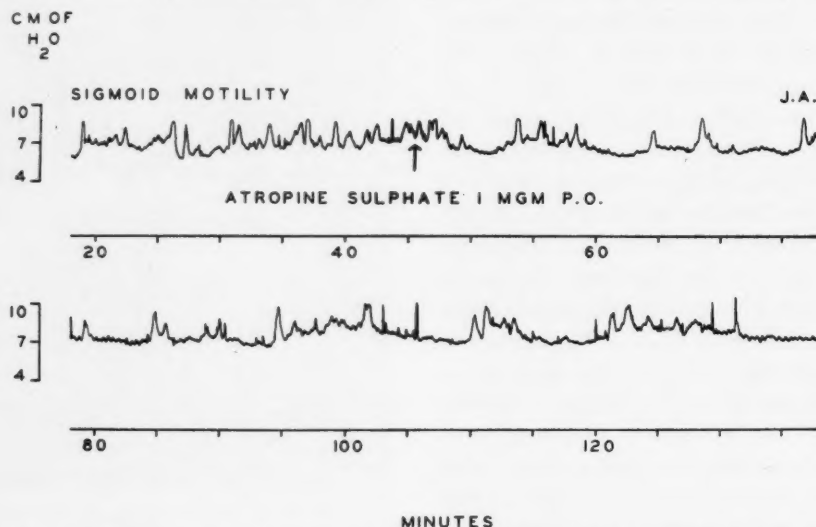


FIG. 3. Here 1.0 mg. of atropine by mouth only slightly modified sigmoid motility.

pine was administered by subcutaneous injection to three subjects; 0.4 mg. did not modify sigmoid motility; 0.6 mg. produced slight diminution for thirty minutes; and 0.8 mg. resulted in considerable depression of activity for sixteen minutes; 0.6 mg. of atropine sulfate by intravenous injection produced a barely perceptible change in one subject; 1.0 mg. intravenously in each of three subjects caused slight to moderate depression of sigmoid motility for thirty to forty minutes in two of them, and abolition of motility in the third subject for five minutes.

It is apparent from these observations that by any route of administration atropine in the usual clinical doses produces only transient and highly variable effects. Most observers agree that atropine in customary therapeutic amounts has some inhibitory effects upon the human colon. The degree of inhibition of motility has varied considerably depending upon the route of administration and the technics of study. Atkinson, Adler and Ivy⁴ found that the subcutaneous injection of 0.7 to 0.8 mg. of atropine sulfate

patients with colonic stomas after the oral administration of 0.65 to 1.3 mg. of atropine.

The action of atropine upon the gastrointestinal tract has been relatively well studied; it is the only agent that has been consistently found by each of several investigators to have an inhibitory action. For these reasons the action of atropine has been utilized as a standard of comparison in the evaluation of other antispasmodics.

Trasentine and *syntropan*, the two most commonly used synthetic atropine substitutes, were tested in man in the usually recommended dosages by Posey et al.⁹ These substances were found to be completely without inhibitory effect upon the motility of the colon and small intestine. Atkinson, Adler and Ivy⁴ also found syntropan to have no influence upon human colon motility. They described some depression of motility by trasentin (75 to 225 mg. orally) but "with the smaller dose no decrease occurred." In a small number of experiments with our technic each of these agents was found to have no significant effect upon sigmoid motility. (Fig. 4.)

The response of the sigmoid colon to *banthine* has been determined in thirty-seven normal human subjects. In each of twenty subjects given 100 mg. by mouth the wave-like contractions of the sigmoid were completely or almost completely

definite diminution of sigmoid activity varying in degree from relatively slight (Fig. 6) to complete abolition of all contractions. In Figure 7 it is apparent that the normal motility pattern returned in sixty minutes. A similar short duration of effect

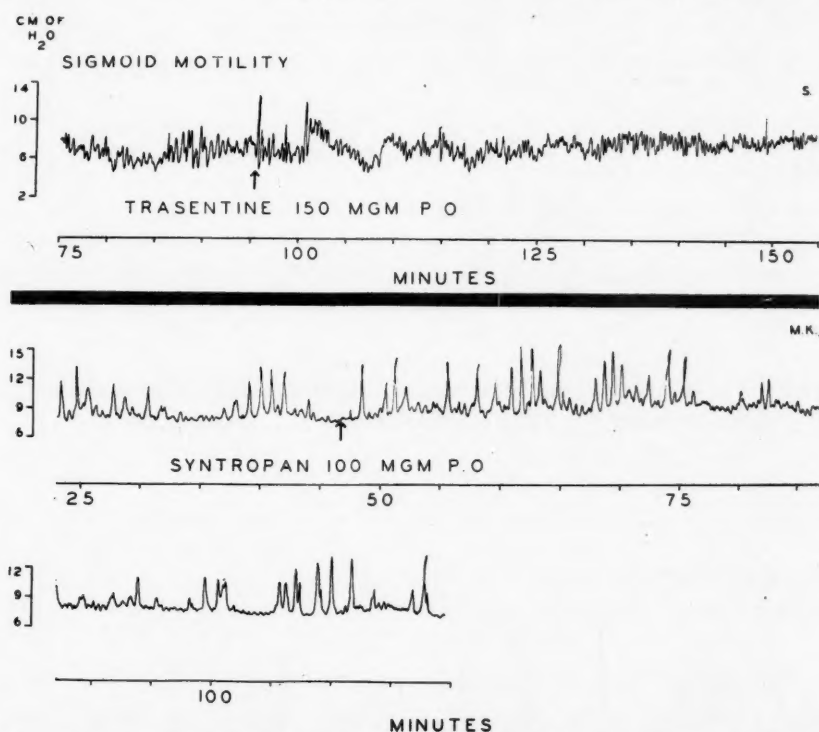


FIG. 4. Trasentine, 150 mg. by mouth, here has no effect on sigmoid motility. Syntropan, 100 mg. orally, is also without effect.

abolished. (Fig. 5.) The interval between administration of the drug and the subsequent alteration of sigmoid motility varied between seven and forty-five minutes; usually the effect occurred in fifteen minutes. The effect usually lasted more than the two hours that the experiments were continued. In only one subject did the sigmoid motility return during the period of observation—this at forty-seven minutes. One experiment was prolonged for five hours and twenty-five minutes without resumption of activity of the sigmoid. When two balloons at different levels in the sigmoid were used, motility was similarly affected in both tracings.

The effect of 50 mg. of *banthine* on colonic motility was investigated in nine subjects. In two of them there was no modification of the motility pattern; in the others there was

has been noted in two other patients who received only 50 mg. orally, but in four the effect continued longer than the duration of the experiment.

Oral doses of 25 mg. have been given to three subjects with almost complete disappearance of sigmoid contractions in two, lasting the entire length of the procedure. It was without effect in the third subject.

The compound has been given *intravenously* to five individuals in doses of 15 to 25 mg. (0.26 to 0.45 mg./kg.). The injections were given slowly over a five- to seven-minute period. There was prompt abolition of sigmoid motility in each experiment (Fig. 7) occurring well before the injection was completed and before the appearance of tachycardia.

The side effects of 100 mg. of *banthine* by mouth have been minimal. All patients ex-

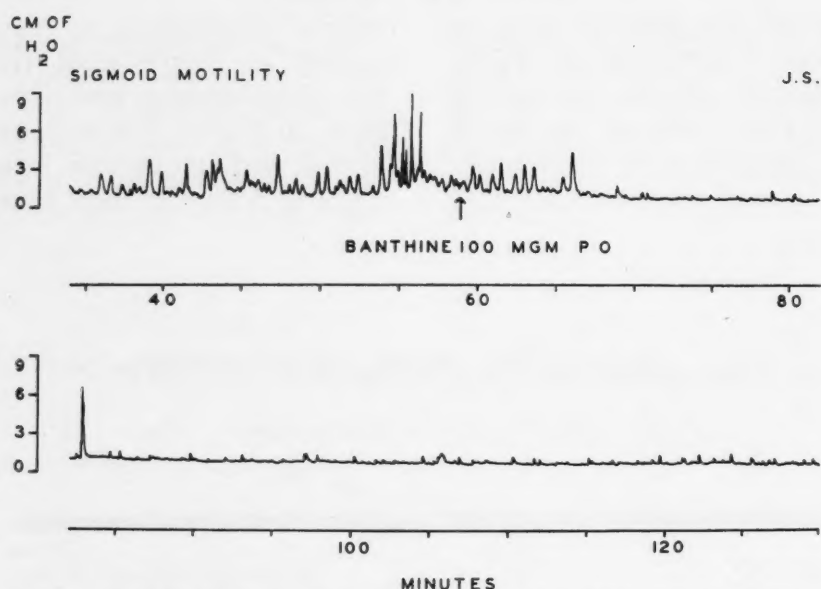


FIG. 5. The effect of 100 mg. of banthine on sigmoid motility. The contractions do not return during the experimental period.

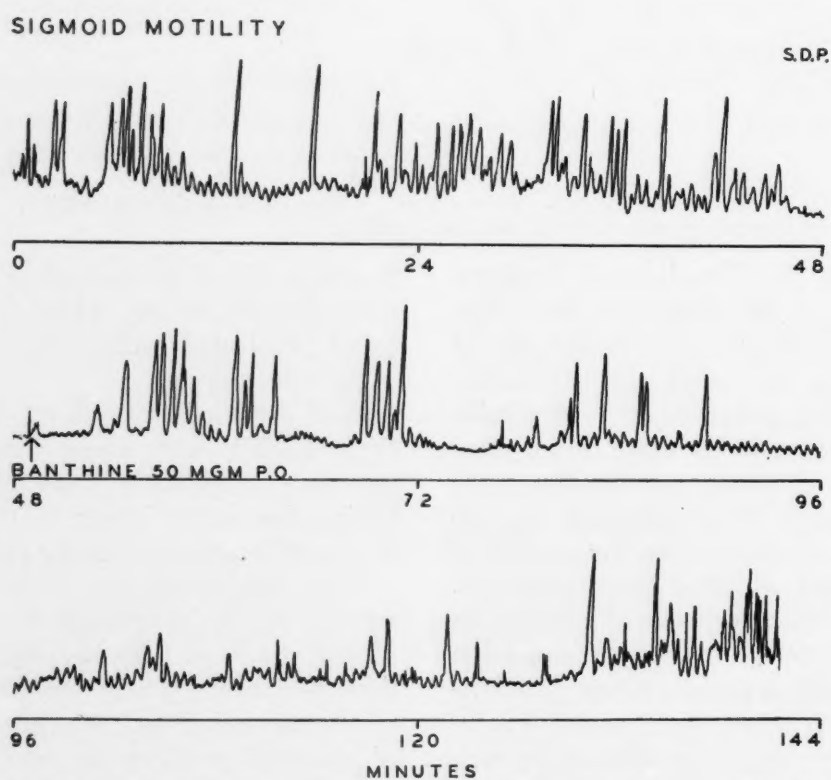


FIG. 6. In this experiment 50 mg. of banthine only partially depressed sigmoid motility. In seven of nine experiments the effect was as great as that of 100 mg.

perienced dryness of the mouth to some degree. This was often very slight. Tachycardia developed in most subjects. The maximum increase in pulse rate was 30 beats a minute and the average rise 17 beats per minute. There was no significant change

colonic motility correlates well with their limited clinical usefulness.

In contrast banthine appears to be an exceedingly potent drug and for many reasons unique. It is the only compound thus far known which has a prolonged

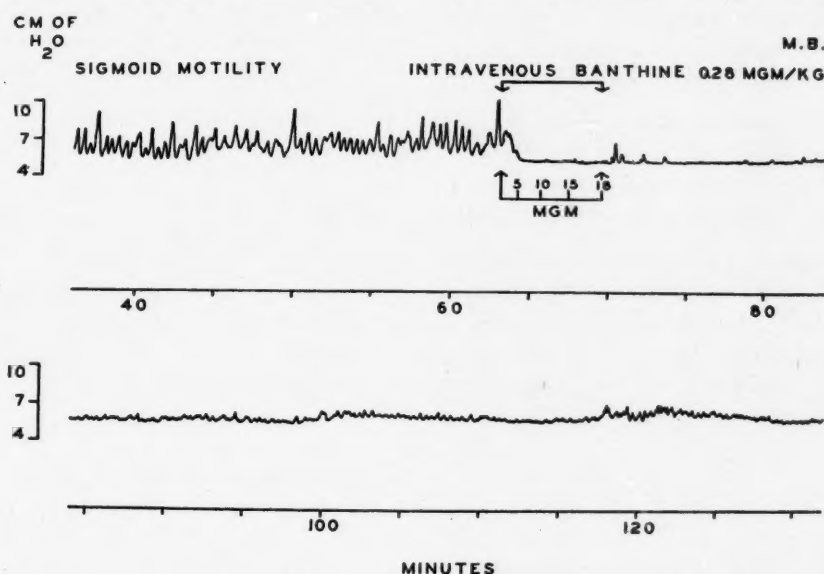


FIG. 7. Intravenous banthine promptly abolishes contractions of the sigmoid. This occurred after only 5 mg. had been administered.

in blood pressure. Although a few patients noted slight blurring of vision, no cycloplegia could be demonstrated. These effects were minimal or absent after smaller amounts of banthine orally. When the drug was administered intravenously, there was usually a considerable but temporary tachycardia.

COMMENTS

These studies indicate that a simple technic such as the one described may be a useful tool in the investigation of bowel physiology in the intact human being. It appears to be a sound method for the evaluation of anticholinergic drugs which are expected to be clinically useful. These sigmoid motility studies have shown striking differences in potency of antispasmodic drugs, all of which have been judged effective by experimental technics involving animals, and they explain the apparently enigmatic clinical failures of some of these potent inhibitors of animal intestine. The inability of the older compounds to diminish human

inhibitory effect on human gastrointestinal motility greatly out of proportion to its effects upon other physiologic processes. It is many times more effective than is atropine in clinically acceptable amounts. Particularly noteworthy is the fact that banthine retains its effect on the colon when it is administered orally. The duration of its action is striking, particularly when compared to the short duration of action of atropine. Sigmoid motility was almost completely abolished in nineteen of twenty experiments for more than the experimental period of two hours after administration of 100 mg. of the drug by mouth. A similarly prolonged inhibitory effect has been observed on gastric motility by Longino⁸ and on small intestinal motility by Chapman.⁵ The side effects of banthine in the amounts used are not hazardous and caused in general only minimal discomfort.

It must be recognized that the method as outlined does not provide entirely adequate data for predicting the clinical efficacy of a

compound. It utilizes only the resting colon as the test object, not the colon subjected to any of its usual stimuli. Among these are the ingestion of food, which evokes a gastrocolic reflex, and environmental stress which may induce changes in colonic motility as part of a physiologic pattern of adaptation. Wolf¹¹ has observed that a number of drugs, including atropine, which have a clearly demonstrable action on the resting human stomach are without effect on the hyperactivity of the stomach which occurs in response to stressful life experiences. Banthine is unquestionably a potent antispasmodic agent, but it is conceivable that the amount necessary to affect the colonic motility pattern of some patients with the irritable colon syndrome may be so great that the side effects of the drug will prohibit its use.

This method of study or a modification of it should continue to be useful in the evaluation of promising antispasmodic compounds. It should be used to complement and extend other experimental technics such as roentgen visualization of the small intestine and balloon studies with Miller-Abbott tubes. A drug which fails to show evidence of potency by these objective tests should be considered inert.

SUMMARY

A simple method for the study of colonic motility in intact human beings is described. By this method orally administered atropine, trasantine and syntropan were found to be without significant or sustained effect on sigmoid motility. The inability of these drugs to inhibit motor activity of the sigmoid may be related to their failure in treatment of functional disorders of the colon.

In thirty-seven individuals a new quaternary amine, banthine (beta-diethylaminoethyl xanthene-9-carboxylate methobromide), profoundly depressed sigmoid motility. Although the data accumulated

by this method are not complete, this agent appears to be much more potent than other clinically acceptable antispasmodic drugs.

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Review

Canicola Fever*

Review, with Report of Two New Cases

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LEPTOSPIROSIS canicola infection in man is infrequently diagnosed in this country. In Holland or Denmark this disease is not uncommon and is well known. In one recent year 240 cases of leptospirosis were reported in Denmark; of these, twenty-four were caused by *Leptospira canicola*.¹

In order to present the subject in its broad aspects it will be divided into a short review of canine leptospirosis, remarks about the organism, a review of the literature on human infection, a discussion of its public health significance and finally a presentation of two new cases of canicola fever.

CANINE LEPTOSPIROSIS

History. Klarenbeek in 1927 described a uremic disease in dogs and was able to find leptospira in their kidneys.² In 1931 Klarenbeek and Schüffner³⁻⁵ cultivated a leptospira from the urine of a Doberman pinscher ill with nephritis. Although morphologically identical with *Leptospira icterohaemorrhagiae*, this dog strain differed in the following properties: It had only slight virulence for guinea pigs; it did not infect white mice and could not be demonstrated in sewer rats; and, most important of all, it was completely different serologically. The agglutination titer of the dog's blood was 1:30,000 against this strain and only 1:100 against *L. icterohaemorrhagiae*. A guinea pig was inoculated with the organism; fourteen days later its blood serum agglutinated the new leptospira up to a dilution of

1:10,000 and agglutinated *L. icterohaemorrhagiae* only up to a dilution of 1:25. This dog strain is now known as *L. canicola*.

The first report of canine leptospirosis in the United States was in 1937 by Davis, Winn and Jungheer.⁶ They described an outbreak of infectious jaundice in a pointer kennel in Connecticut. At autopsy leptospira-like organisms were seen in the lungs, liver and kidneys. Urine culture grew a strain characterized by low virulence for guinea pigs.

Epizootiology. Sixty per cent of over 900 reported cases of canine leptospirosis were caused by *L. canicola*;⁷⁻¹⁵ the more recent investigations of epidemics disclose a much higher percentage. It is believed that in the United States the great majority of canine leptospirosis is due to the canicola strain.¹⁶ In some parts of the Midwest it would seem that *L. icterohaemorrhagiae* is the predominant cause^{12,14,15} but this is not settled.¹⁷ Although the dog is susceptible to infection with thirteen distinct strains of leptospira,^{18,19} *L. canicola* and *L. icterohaemorrhagiae* account for almost all cases of canine leptospirosis and are the only species transmissible to man.

The distribution of canine leptospirosis is worldwide. It has been reported from almost all countries of Europe, many parts of Asia, the East Indies, Australia, the Hawaiian Islands, Belgian Congo, Argentina, the West Indies, Mexico, Canada and every section of the United States.

Leptospirosis in dogs is a common disease.

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A total of 4,800 dogs selected at random were tested by serologic methods; an average of 27 per cent of these apparently healthy dogs had diagnostic agglutination titers.^{1,5,8,11,13,17-34} In some series the percentage of positive tests was up to 40 to 46 per cent. Of over 2,000 dogs brought to veterinarians' clinics because of various maladies, an average of 35 per cent had significant agglutination titers and in some reports the percentage of dogs with positive titers was as high as 50 to 65 per cent.^{1,5,20,28,35-38} All breeds are equally susceptible. No age is exempt. The disease is rare, however, under one year of age. The incidence of infection increases progressively with the age of the dog. About 50 per cent of dogs over six years of age are estimated to show the residuals of a latent infection.⁸ Male dogs are infected about three to five times as frequently as bitches.

Clinical Features. The clinical picture of canine leptospirosis has been adequately described many times.^{9,13,35,39-41} There is no longer any doubt that canine typhus, Stuttgart disease, acute infectious jaundice (yellow kennels) and Weil's disease of dogs are all manifestations of the same disease.

Two forms may conveniently be described, namely, the icteric type and the hemorrhagic type with or without azotemia. Either form may show features of the other or may change completely into the other type. Both *L. canicola* and *L. icterohaemorrhagiae* may produce either picture although *L. canicola* more commonly causes the hemorrhagic-azotemic type and *L. icterohaemorrhagiae* the icteric type. The not infrequent cases in which acute uremia without jaundice and hemorrhages, or asymptomatic chronic nephritis, is the predominant feature⁴² are usually due to *L. canicola*.

The severity of the illness and its course vary. An appreciable number of cases run a mild course and these dogs may be asymptomatic; most are severe and not uncommonly are fatal in about a week; and a few have a fulminating course with death in a day or two. Klarenbeek¹¹ found that

chronic cases equalled in number those with an acute course. In an epidemic the mortality may be as high as 95 per cent.

Icteric Form: The clinical syndrome is characterized by acute onset of high fever, jaundice after two to five days, skin and mucous membrane hemorrhages and death in several days to a week. Autopsy⁴³ shows generalized icterus and petechial hemorrhages, tubular degeneration and capillary congestion of the kidneys, congested gastrointestinal mucosa and inflammatory and necrotic changes in the liver.

Hemorrhagic-azotemic Form: This clinical picture presents sudden onset of high fever, lameness of the hind limbs, depression, often subnormal temperature on the second or third day, dehydration, ulcerative stomatitis, bloodshot eyes, bloody vomitus and bloody, foul diarrhea, skin and mucous membrane hemorrhages, rising azotemia usually, polyuria or anuria and death in three to ten days. In both forms of the disease there is polymorphonuclear leukocytosis and the urine contains albumin, casts and red and white blood cells. Autopsy^{44-46,61} discloses generalized petechiae, predominantly inflammatory renal changes but with well marked degeneration and desquamation of the tubular epithelium, hemorrhagic gastroenteritis, degenerative muscle lesions and similar but less intense liver changes (usually present). Even in *L. icterohaemorrhagiae* infections renal, not hepatic, lesions are constant.⁴⁸

Animals that have recovered are said to be immune to reinfection up to about five to six years.⁴⁹

LEPTOSPIRA CANICOLA

Morphologically, *L. canicola* is identical with *L. icterohaemorrhagiae*, even under the electron microscope.⁵⁰ The organism is 4 to 10 or more micra in length, 0.07 to 0.14 micra in width, has spirals about 0.25 micra wide and 0.3 to 0.6 micra in pitch and shows a characteristic hook at one or both ends. Like other leptospira, organisms obtained from culture may exhibit a pear-

shaped swelling at one end with loss of the terminal curvature.⁵¹⁻⁵³

Leptospira have remained viable and virulent after 585 days on artificial media and for at least twenty-two days in surface water. They are quickly killed, however, by strong sunlight, salt water and acid solutions.⁵⁴

The best culture medium is Schüffner's modification of Verwoort's medium, a highly buffered peptone-serum preparation.^{13,20} Growth may be present within a week but rarely may be delayed for five to six weeks. Other media have been described recently⁵⁵⁻⁵⁷ but have not yet been evaluated.

Unlike *L. icterohaemorrhagiae* which is known to infect many animals, *L. canicola* in nature infects only the dog and no other animal. Experimentally, rats, mice, rabbits and cats are practically unaffected by inoculation of virulent *L. canicola* organisms. Guinea pigs show very little susceptibility on first passage and increasing virulence of the organism on repeated passages. Morton⁵⁸ first reported the high susceptibility of young hamsters to *L. canicola* infection. This was soon confirmed.^{59,60}

CANICOLA FEVER

Epidemiology. The first case of leptospirosis canicola in man was reported by Schüffner⁴ in May, 1934, from Holland. Meyer and his associates⁴⁷ described the first two cases diagnosed in the United States in 1939.

Although a large number of dogs in many parts of the world have become infected with *L. canicola*, only 198 proved cases of canicola fever have been reported. (Table I.) The two cases to be described bring the total to 200 cases.

The human infection is derived from diseased dogs. *Leptospira* are excreted in their urine for several weeks to several months. The organisms in a dog's urine get into man's blood stream by penetrating either broken skin or intact mucous membrane after ingestion. *L. canicola* is said not to pass through intact skin. There is no

record of human-to-human transmission of the disease although this appears to be feasible. Molner and his colleagues⁷⁴ raise the possibility that rats act as agents in the transmission of this disease in those cases in which exposure to rats and none to dogs is

TABLE I
REPORTED CASES OF CANICOLA FEVER

Country	No. of Cases
Holland ^{4,5,9,62-68}	49
Denmark ^{1,69,70}	47
Germany ⁷⁷⁻⁸¹	39
Switzerland ^{10,63,71}	18
U. S. A. ^{16,22,27,47,72-76}	13
France ³²⁻³⁸	12
Argentina ⁸⁹⁻⁹²	7
England ^{25,93,94}	6
China ³¹	2
Austria ⁹⁵	1
Norway ⁹⁶	1
Puerto Rico ⁹⁷	1
Hawaii ⁹⁸	1
Italy ⁹⁹	1
Total	198 cases

found. One reported case occurred in a swineherd.¹⁰⁰ There is no evidence, however, that rats or pigs are carriers of *L. canicola*.

In 131 of the reported cases mention is made of the presence or absence of a likely source of infection. There was close contact with dogs in eighty-six, or 66 per cent, of the 131 cases. About three-fourths of these dogs were proved to have leptospirosis canicola; at that time about one-half of them were ill and the other half were apparently healthy dogs. In an additional thirteen cases the possibility of contamination with infective canine urine is present, such instances being canine leptospirosis in the vicinity, swimming in a river or canal, drinking river or canal water and playing in ditches.

Of the reported cases, males slightly exceeded females in number. Fifty-six per cent of cases were in men. The disease may occur at any age but it was rare in children under ten years. The average age of the patients was about thirty-three years.

Infection has occurred in every month. Three-fourths of reported cases took place between July and December. The incuba-

tion period is unknown but is assumed to be similar to that of Weil's disease, namely, one to two weeks. However, the range of probable exposure of the reported cases to leptospiruria was between seven to forty-one days.

TABLE II
FREQUENCY OF MANIFESTATIONS IN CANICOLA FEVER*

Symptoms	Per cent
Fever.....	100
Sudden onset.....	90
Prostration.....	87
Headache.....	80
Myalgia.....	70
Chills.....	52
Gastrointestinal symptoms.....	51
Mental symptoms.....	29
<i>Signs</i>	
Injected conjunctivae.....	48
Meningeal signs.....	48
Renal findings.....	39
Bradycardia.....	39
Hypotension.....	20
Bleeding tendency.....	20
Coated tongue.....	19
Respiratory findings.....	19
Sore throat.....	19
Rash.....	15
Icterus.....	13
Palpable liver.....	8
Lymphadenopathy.....	8
Herpes labialis.....	5
Palpable spleen.....	2.4
<i>Laboratory Findings</i>	
Rapid sedimentation rate.....	100
Albuminuria.....	75
Spinal fluid changes.....	42
Leukocytosis.....	41
Microscopic hematuria.....	36
Azotemia.....	32
Cylindruria.....	30

* It is important to point out that these percentages are only rough approximations and should not be taken too literally. Many of the reported cases are not described in the fullest detail; only about 100 cases lend themselves to this analysis.

Clinical Features. The physician may be called to see an adult acutely ill and prostrated for two or three days with high fever, repeated shaking chills, headache, vomiting and generalized muscle pains. Examination discloses markedly injected conjunctivae, coated tongue, tender muscles and perhaps hypotension or bradycardia in the presence of a high fever. The remainder of the physical examination is apt to be non-contributory. At this time or within several days meningeal signs may develop. The urine contains albumin. The hemogram

may be normal or may show a moderate elevation of the white blood cells with a pronounced shift to the left. This is the typical early clinical picture; not a few cases lack some of these characteristic features or exhibit additional symptoms and signs.

The frequency of the symptoms and signs in the reported cases of canicola fever are listed in Table II. The great majority of cases began acutely with fever between 101° to 104°F., chills, headaches, generalized myalgia and often gastrointestinal symptoms.

All cases presented fever. In two-thirds of patients the initial recorded temperature was 103°F. or over, and in about half of all patients it was 104°F. or over. The type of fever encountered is variable; it may be remittent, septic, undulatory or sometimes sustained. The duration of fever was usually less than seven days. About one-third of patients had fever for from seven to thirteen days. Only a few instances of fever persisting for more than two weeks are recorded; one patient, however, was febrile for seven weeks.⁶³

Early in the course prostration was common and often fairly severe. Occasionally this feature was lacking completely. Most patients complained bitterly of severe, constant headache. The site was not uncommonly frontal but more often the headache was diffuse without localization. The duration of headache usually paralleled that of the elevation of temperature. Most commonly all muscles were painful and tender but in about 20 per cent of those with myalgia one or several muscle groups were singled out as being particularly distressing. In order of decreasing frequency these were back and loin, calf, neck and limb muscles in general. Arthralgia was quite prominent at times. Soon after the onset of illness true shaking chills occurred. Repeated chills were the rule.

Anorexia was found in almost all cases. Over one-third of patients vomited and about 20 per cent of them suffered from constipation and/or abdominal pain. Often the abdominal pain was actually muscular

pain originating in the abdominal wall. Diarrhea was relatively uncommon, being mentioned in about 10 per cent of patients; it was bloody in one case.⁹⁷

The most common mental aberrations were drowsiness, irritability, delirium and confusion. Others, less common, were convulsions, agitation and stupor. These manifestations were only slightly more prominent in those cases with evidences of meningeal irritation.

Both the palpebral and bulbar conjunctivae were usually intensely injected. There was no discharge from the eyes. This sign and tender, painful muscles often first created suspicion of a leptospiral infection. When meningeal signs were present, marked photophobia was not uncommon.

As a rule mild acute nephritis developed, apparently mainly affecting glomerular function. The nephritis was characterized by oliguria, albuminuria, cylindruria, microscopic hematuria, low urea clearance and slight to moderate azotemia. The blood urea nitrogen rarely rose over 60 mg. per cent, the azotemia usually persisting for only one to three weeks. However, in one case a peak of 140 mg. per cent is recorded on the sixty-third day of illness.⁷⁰ Albuminuria for longer than one month has been reported in ten per cent of patients with nephritis. Chronic nephritis has not resulted in any case.

A slow pulse was often a striking and surprising finding, e. g., a pulse of 84 in the presence of a fever of 103.5°F.⁶⁴ and again a pulse of 86 with a fever of 105°F.²⁵ There was apparently no relationship between bradycardia and elevated spinal fluid pressure, jaundice or hypotension. Whenever a systolic blood pressure of 100 mm. Hg or below was noted, there was usually evidence of marked prostration and almost invariably a fever of 103°F. or higher.

Epistaxis was a common manifestation. Sometimes gross hematuria occurred; it may be the chief complaint. In one case there was bleeding into the bowel and from the gums;⁹⁷ in another, oral mucosal petechiae.⁹⁴ Dutch authors in particular have com-

mented upon the unusual frequency of finding a thickly coated tongue in a patient who has been ill for only a day or two.

Respiratory manifestations most often took the form of bronchopneumonia, usually basal in location. A few patients had acute bronchitis or tracheobronchitis. Pharyngitis was of a mild nature in almost all cases. No one had a pharyngeal membrane.

An exanthem without an enanthem was described by observers in Europe and Argentina. The rash was usually morbilliform, sometimes scarlatiniform or an admixture of both forms; rarely did it resemble erythema nodosa. Itching and scaling were absent. The eruption appeared suddenly on about the third or fourth day of illness, first and most extensively on the trunk but was also present on the limbs and sometimes on the face; its duration was usually fleeting, lasting hours to a day but on occasion from two to five days.

Jaundice was not frequent. It was present in 13 per cent of 173 cases. Usually the icterus was mild in intensity and short in duration, involving only the sclerae for about a week. When the icterus was marked, the liver was apt to be enlarged and palpable. In no jaundiced patient was the spleen palpable. Only half of the patients with palpable livers were jaundiced. Usually the enlarged liver was not tender and in no case did the liver edge descend more than two fingerbreadths below the right costal margin. A non-tender splenic tip was palpated a few times. Both an enlarged liver and spleen occurred once, in a non-icteric patient.

A generalized, not striking lymphadenopathy was mentioned in several cases. It was not associated with a palpable liver or spleen.

Herpes developed in about 14 per cent of patients with meningeal signs. The combination of herpes labialis and meningitis, according to certain British clinicians, suggests the possibility of leptospiral meningitis.

Although an arbitrary distinction, it is helpful to differentiate between a *grippe type* of canicola fever, which has been described

in the foregoing section, and a *meningeal form* of the disease. Gaillemin⁸³ would add gastrointestinal and encephalitic types. However, a division between cases with and without meningeal signs is adequate.

All cases of canicola fever described in the literature began in exactly the same way, with fever, chills and headache. However, in about one of every two patients distinct meningeal signs developed and dominated the clinical picture. The onset of the meningeal signs and symptoms may be at the onset of the illness but occurred much more commonly between the second and fifth day (and up to the ninth day). The duration of meningeal irritation was on the average about ten days. Although these cases were very similar in other respects to those without the meningeal picture, there were some differences: slightly younger patients; higher incidence of headache, photophobia and herpes labialis; and twice as common occurrence of bradycardia and gastrointestinal symptoms.

On the other hand, the grippe type of case was in comparison characterized by a slightly longer duration of fever and higher incidence of chills, rash, hypotension and palpable liver. Jaundice was four times as common. There appear to be no significant differences between the grippe and meningeal types as regards incidence of injected conjunctivae, myalgia, hemorrhagic tendency and renal involvement.

Laboratory Findings. Leukocytosis was much more common in the grippe type of case. A count of over 20,000 cu. mm. was rare. An increase of polymorphonuclear cells (over 70 per cent) was present in 70 per cent of the initial differential smears. In about one-half of the smears there was a shift to the left (over 5 per cent stab forms), in not a few instances down to the myelocyte level. Eosinophilia of 4 to 12 per cent was noted in 25 per cent of the smears. The hemoglobin content and red blood cell count are not affected during any phase of the disease. A moderately rapid to very rapid erythrocytic sedimentation rate is found without exception.

Albuminuria was usually present in the cases described in the literature. On microscopic examination the finding of many hyaline and granular casts or many red blood cells in the urine was not uncommon. Sometimes numerous unclumped white blood cells were seen. These abnormalities cleared up within one week usually.

In the presence of icterus liver function studies indicated an active hepatocellular process. The highest icterus index recorded was 129. In the absence of icterus it is interesting to note that the van den Bergh reaction may be immediate direct, the serum bilirubin above normal limits and the tests of liver function similar to those seen in acute hepatitis.

Bleeding, clotting, clot retraction and prothrombin times, platelet count and Rumpel-Leede test were usually normal. Occasionally the platelets or prothrombin percentage was slightly lower than normal but not below the "critical bleeding level." Blood serology, total serum protein and albumin-globulin ratio were unchanged. The occurrence of azotemia has been mentioned.

Initial lumbar puncture yielded spinal fluid characterized by clear or turbid appearance, under normal pressure usually, positive Pandy reaction and slightly increased protein (rarely up to 400 mg. per cent), normal to moderately lowered sugar but not below 35 mg. per cent, normal chlorides and pleocytosis. The cell counts ranged from 12 to 2,450 cells per cu. mm. but more than half fell between 12 and 200 cells. It is interesting to note that polymorphonuclear cells predominated in as much as 40 per cent of the differential counts. Subsequent spinal taps usually showed an increase in the number of cells and a tendency toward an increase in the percentage of mononuclear cells during the second week of the disease. Thereafter the number of cells rapidly decreased and became normal in another week or two. These characteristic spinal fluid changes were found in one case with confusion, delirium and stupor without any meningeal signs;⁷⁶

this may be an example of leptospiral encephalitis.

Course. The course of canicola fever is variable. The acute febrile phase of the illness was usually over within one to two weeks and some patients convalesced rapidly. About 40 per cent of patients recovered completely within two to three weeks. However, this was not the more common course. Many writers have pointed out the slow and prolonged convalescence characterized by many weeks or months of symptoms, chief of which is extreme weakness. In other cases headache, muscle pains (especially of the back), faintness and recurrence of fever may be distressing. Indeed, in some 45 per cent of cases convalescence was not completed until after two, three or even four months. Febrile relapses are frequent. About one of every two patients experienced a return of fever during convalescence, with or without a recurrence of any or all previous symptoms. Half of the relapses started between the fourteenth and eighteenth day after onset. Fifty per cent lasted one to five days; three-fourths, nine days or less. Further febrile relapses were rare.

Only two instances of recurrence were mentioned.^{73,93} Both resembled mild, abortive attacks of the original illness, one occurring two months after the initial attack and the other six months later. It is noteworthy that penicillin was used in the initial treatment of both cases.

Complications. Complications developed in some 15 per cent of patients. Almost always the complications were mild, transitory and inconsequential. The most common one was temporary alopecia, partial or complete. Others were ocular disturbances (such as iritis, choroiditis, uveitis and vitreous opacity), myocarditis, psychosis, muscular paresis, sciatica, sphenopalatine neuralgia and parotitis.

Mortality. Three deaths have been attributed to this disease.^{74,94} The one described in detail was due to uremia.

Comparison with Weil's Disease. As a rule canicola fever is an abbreviated, much

milder, less serious infection than Weil's disease. This applies to almost all features of the two diseases: the initial prostration; the frequency and severity of myalgia, gastrointestinal symptoms, mental symptoms, renal involvement, respiratory manifestations, hemorrhagic phenomena and icterus (seen in 50 to 67 per cent of cases of Weil's disease); frequency and degree of leukocytosis; duration of illness; number and seriousness of complications; and fatality rate.

Canicola fever is characterized by the following, in contrast to Weil's disease: a larger number of female patients; a much lower incidence of jaundice; a higher frequency of meningeal signs and of febrile relapses; and a much milder illness. Nonetheless, it is doubtful if in individual cases a differential diagnosis could be made early between the two diseases without laboratory aid.

Mechanisms of Symptoms and Signs. From what is known about leptospiroses in dogs, experimental animals and humans, it may be possible to explain certain clinical aspects of canicola fever. With regard to myalgia, minute hemorrhages and small degenerative foci have been described in the striated muscles in Weil's disease.^{101,102} They are present in the muscles of dogs infected with *L. canicola*⁴⁵ and presumably in those of humans as well. The gastroenteritis described in dogs could account for the symptoms of anorexia, nausea, vomiting, abdominal pain and diarrhea which are commonly seen in humans.

In several cases of Weil's disease spirochetes were recovered from the spinal fluid. It might be assumed that during the early septicemic stage leptospira penetrate the meningeal barrier and incite serous meningitis.

Cerebral manifestations of the disease apparently are the result of a combination of pyrexia, meningitis and possibly some degree of encephalitis.

The kidneys of animals and humans dying of leptospiral infections show interstitial nephritis with tubular degenerative

changes. In canicola fever the clinical evidence strongly suggests both glomerular and tubular damage, supposedly toxic in origin due to the organisms themselves. Acute interstitial nephritis was found at autopsy of a patient dying of canicola fever.

The bleeding tendency appears to be due to primary capillary damage and not to any disorder of the blood or clotting mechanism.¹⁰³ The conjunctival injection is commonly included under this heading.

There is every reason to believe that icterus results from leptospiral hepatitis unassociated with any hemolysis or extra-hepatic biliary tract obstruction. It is probable that mild anicteric hepatitis occurs much more commonly than is reported.

Differential Diagnosis. Canicola fever is not often thought of in the differential diagnosis of an acute febrile illness without jaundice. When considered it may not be possible to prove or disprove the diagnosis until the patient has entered the convalescent period; but if the clinical features of canicola fever were sufficiently well known so that a presumptive diagnosis could be made, many a patient would be spared a severe illness by prompt treatment.

This disease should be thought of under the following circumstances: (1) canine leptospirosis in the neighborhood; (2) any febrile illness of a veterinarian or dog handler; (3) "grippe" or meningitis in an adult with a sick (or well) dog in the household; (4) an acute illness with high fever, chills, headache, intensely injected conjunctivae and tender, aching muscles; (5) an acute febrile illness with repeated chills of unknown etiology; (6) fever of undetermined origin accompanied with myalgia or injected conjunctivae and negative blood cultures; (7) an acute febrile illness (with any of the aforementioned features) followed in two to five days with serous meningitis; (8) serous meningitis with herpes labialis; (9) any obscure meningitis; and (10) any febrile jaundice.

In the presence of any of these situations a question or two concerning a possible source of contact with *L. canicola* may

strengthen the clinical impression. However, in about one-third of the reported cases the source of infection could not be determined.

Although canicola fever may be suspected clinically, the diagnosis must be established in the laboratory.

It is interesting to note the initial diagnoses of a dozen cases of canicola fever in one report: epidemic meningitis (five times), grippe (three times), typhoid fever (two times) and poliomyelitis (two times). Canicola fever is most frequently misdiagnosed as one of these four diseases. Pyogenic meningitis may not be difficult to exclude after spinal fluid study but many of the serous meningitides (such as mumps, herpes, choriolymphocytic or tuberculous meningitis) may be impossible to differentiate clinically.

In this country most cases of canicola fever are not recognized unless the patient becomes jaundiced. Infectious hepatitis (viral type) then enters into the differential diagnosis, but canicola fever may be suggested by absence of prodrome, sudden onset with high fever and chills, shorter duration and milder intensity of jaundice, absence of splenomegaly and presence of meningeal, muscular and nephritic manifestations. Occasionally one of the following diseases may also have to be considered: acute gastroenteritis, acute meningococcemia, infectious mononucleosis, acute glomerulonephritis or pyelonephritis, septicemia and a blood dyscrasia.

SPECIFIC DIAGNOSIS

Of the various methods employed to diagnose infection with *L. canicola* (or the other leptospira), animal inoculation and the agglutination-lysis test are considered the most reliable and are most used.

When attempting to demonstrate leptospira by animal inoculation, darkfield or cultivation, the patient's blood is used during the first week of illness, or urine from about the tenth day to the fourth or fifth week of illness.

Animal Inoculation. Guinea pigs or preferably young hamsters are injected with the

patient's blood or urine (or growth from culture medium). As early as forty-eight hours after inoculation cultures made from heart's blood of the latter animals become positive. Usually the animals die in eight to ten days and show widespread hemorrhages at autopsy. (Hamsters infected with *L. icterohaemorrhagiae* all die in about five days with generalized hemorrhages and jaundice.) *Leptospira* may be demonstrated in the liver, kidneys and other organs.

Serologic Tests. Specific agglutinins, lysins and complement-fixing antibodies appear in the blood toward the end of the first week of illness. Artificially infected dogs build up a diagnostic titer between the sixth and eleventh day.¹⁰⁵ Humans usually do not show a diagnostic titer until between the tenth and fourteenth day of illness. However, five of the reported cases^{25, 63, 64, 80} and one to be described were found to give positive tests as early as the seventh to ninth day of illness. The agglutinins and lysins increase in amount rapidly to reach a maximum level within three to eight weeks. The antibodies persist in high titer for many months and then gradually decline to a titer of about 1:300 within one to three years. They remain at about this level for an unknown number of years.

The agglutination-lysis test universally used is that described by Schüffner and Mochtar.¹³ Living or freshly formalinized organisms of four- to five-day old cultures are the antigen; sterile, non-hemolyzed blood serum of the patient supplies the antibodies. Agglutination takes place when the patient's serum is mixed with the organisms, and lysis of the organisms occurs when the end point of the reaction is reached. There may be cross agglutination between *L. canicola* and *L. icterohaemorrhagiae* or *Leptospira hebdomadis*. Occasionally the titers against each organism may be identical, especially early in the disease when the titers are relatively low. At this point the absorption test of Ruys and Schüffner¹⁰⁶ may be used to distinguish between the two with considerable success. Without the absorption test one or more weeks may elapse

before it is possible to identify the causative leptospira. The microscopic technic is the one used unless otherwise stated; a diagnostic titer is considered to be 1:300. The less sensitive but more rapid macroscopic or plate method is widely used by veterinarians; with this technic a significant titer is 1:100. Demonstration of leptospiral antibodies in the cerebrospinal fluid and urine is often possible but has no practical value because the titers are considerably lower than that found in the blood at the same time.

The complement-fixation test and the adhesion test are not as valuable as the agglutination-lysis reaction and are not generally used.

Darkfield Examination of Blood and Urine. Darkfield examination of blood is rarely positive, both in dogs and in humans.^{13, 16, 75, 76} "Pseudospirochetes," probably resulting from fibrin and degenerating blood cells and platelets, are particularly confusing; they have been seen in a high percentage of normal bloods and are especially frequent in any febrile or icteric disease.¹⁰⁷⁻¹⁰⁹ For this reason it is best to use defibrinated blood for darkfield study.

Leptospira may be found in fresh, centrifuged urine at a pH of 7.0 or slightly higher. Darkfield examination of such urine is frequently positive. In the presence of hematuria "pseudospirochetes" may be seen in the urine also.

Culture. Blood and urine may be cultured at an optimum temperature of 32 to 35°C. Unfortunately growth may be delayed for several weeks. This method is not widely used routinely.

Procedure in a Suspected Case. The routine outlined by Minkenhof⁶³ is adequate. If the patient has been ill for less than seven or eight days, there is a fair chance of cultivation of leptospira in the guinea pig or hamster or on Schüffner's modification of Verwoort's medium within an additional three to seven days, after which the type can be determined serologically. If the patient has been ill for longer than seven or eight days, the agglutination-lysis reac-

tion can be relied upon. Darkfield study of blood or urine may be attempted but negative results should not be accepted with finality, and positive results must be verified.

TREATMENT

Before the advent of antibiotic therapy treatment of canicola fever was symptomatic and supportive. This included rest, sedation, high caloric diet, analgesics, abundant fluids and occasionally small blood transfusions. Specific therapy is available in the form of immune or convalescent serum, both of which benefit experimental infection with *L. canicola* in mice and hamsters when given before the fourth day and the natural infection in dogs before the tenth day of illness.^{59, 110, 111} Serotherapy has not been used extensively in canicola fever.

The consensus is that sulfonamides experimentally and clinically are of no value against leptospirosis canicola and may even be detrimental although the success of Snapper and his co-workers³¹ with sulfanilamide in two cases should be mentioned.

Penicillin has definite value in the treatment of *L. canicola* infections. *In vitro*, penicillin is leptospirostatic, completely inhibiting either *L. canicola* or *L. icterohaemorrhagiae* in concentrations as low as 0.4 to 0.5 U. per cc. of culture medium, but it is not leptospirocidal in concentrations as high as 500 U. per cc.¹¹²⁻¹¹⁵ Neither of the organisms produces penicillinase. Experimentally infected mice, guinea pigs and hamsters are protected against *L. canicola* and *L. icterohaemorrhagiae* when penicillin is administered before clinical symptoms appear, i.e., up to the third day after inoculation.^{110, 113, 116-119} Antibody formation is not interfered with. Canine leptospirosis is now treated principally with penicillin. In those cases in which the antibiotic is started early in the disease results have usually been clear-cut and often life saving.^{36, 120-123} Leptospiruria is significantly decreased. Over sixty cases of Weil's disease in man have been treated with penicillin.¹²⁴ Most workers who gave the drug early in the illness have been satisfied that beneficial ef-

fects and sometimes dramatic cures were obtained, although not invariably.^{99, 117, 124-136} Penicillin therapy has been used in twelve cases of canicola fever so far.^{25, 73, 75, 78, 79, 94, 97, 99} Results were excellent in five cases, fair in three and poor in four. In those instances in which penicillin was given early there was usually a rapid subsidence of fever, symptoms and signs with a rapid recovery. Febrile relapses, however, were not prevented in three cases.

Streptomycin has been shown to be as effective as penicillin *in vitro* against *L. canicola* and *L. icterohaemorrhagiae* and in protecting hamsters against *L. icterohaemorrhagiae*.^{115, 118} The suggestion has been made that streptomycin may be useful as an adjunct to penicillin in the treatment of leptospiral infections.

The type of immunity resulting from canicola fever, if any, is unknown. No reinfection has been reported, however.

PUBLIC HEALTH ASPECTS

The reservoir of canine leptospirosis from which canicola fever and occasionally Weil's disease^{137, 138} may stem is large. It is estimated that 4 to 15 per cent of dogs the world over show the residuals of leptospirosis and that about 25 per cent of dogs in this country have or have had latent leptospirosis.^{5, 13} All agree that dogs excrete leptospira usually for four to six weeks after the onset of infection but sometimes for much longer periods. Walch-Sorgdrager⁵ observed leptospiruria for four months in some dogs. Prolonged excretion of leptospira is associated with the development of chronic nephritis, which is not at all infrequent.^{9, 11, 32} Jones and his associates²⁴ autopsied forty-eight asymptomatic healthy young dogs with positive agglutination tests. They found a subacute form of interstitial nephritis in 93 per cent of these dogs; 12.5 per cent of silver-stained kidney sections showed leptospira; and the organisms were cultured from the urine of 11 per cent of these apparently healthy animals before they were killed. Meyer and his workers¹³ believe that from 20 to 50 per cent of infected dogs in

this country become temporary or permanent leptospira carriers and shedders.

Some believe that in view of the large canine reservoir human infection with *L. canicola* must be more common than is appreciated. Doubtless, an unknown number of cases are misdiagnosed as gripe, gastroenteritis, non-paralytic poliomyelitis and the like. Some cases are so mild that only special awareness of canicola fever could suggest the correct diagnosis. One patient was slightly unwell for two days.⁶³ The presence of many subclinical cases, especially in those in close contact with dogs, has been suspected but has not been borne out by serologic testing. Of an aggregate of over 1,300 sera tested against *L. canicola*,^{22,98,139-141} including seventy-three sera from persons in very close contact with dogs, only one had a positive agglutination test, a titer of 1:300 in a city park attendant. This work strengthens the view that man has a low susceptibility to *L. canicola* infection.

Canicola fever is an occupational hazard to those who work with dogs. The occupations of some of the patients included dog breeder, veterinarian, veterinarian's assistant and laboratory worker. Fifteen per cent of reported cases occurred in such persons.

Prevention of canicola fever begins with control of canine leptospirosis by alertness for the canine infection by dog owner, veterinarian and physician, isolation of the infected dog, prompt treatment with antibiotics, and return of the dog to his owner only after leptospiruria has ceased. Active immunization of dogs with formalized leptospira antigen experimentally has had good results.^{142,143} Precautions for humans that might be used to advantage include avoidance of swimming in rivers and ponds or of drinking water in areas where the canine disease is common; care in handling the excreta of dogs with unexplained illness or dysuria; protection of those exposed to infection by virtue of their work (water-tight boots, hand and arm coverings, quick care for skin abrasions, etc.); and disinfection of patients' urine with acid. There is no

prophylactic vaccination for humans against *L. canicola*.

CASE REPORTS

CASE I. J. P., a seventeen year old colored male, was admitted to the isolation service of Gallinger Municipal Hospital on September 20, 1946, as a poliomyelitis suspect with a two-day history of fever, headache, pain and weakness of the legs. Sore eyes developed three days before admission. The patient noticed sore throat and aching of the thigh muscles two days before admission. He went to bed and became aware of warmth and sweating. One day before admission his legs gave way on attempting to get out of bed. On the day of admission he experienced severe generalized headache. All other symptoms were denied. He had been swimming in the Potomac River four days before admission, as he had frequently done the whole summer. His occupation was that of a helper on a trash collection truck. About one month previously he had handled cats and dead rats. He owned a dog which had not been ill.

Physical examination revealed a well developed and well nourished, young colored male, who appeared to be in no distress and not acutely ill. His temperature per rectum was 102.8°F., pulse 80, respirations 22 and blood pressure 120/75. Positive findings were photophobia, moderately injected conjunctivae, bilateral hamstring spasm, questionable weakness of the abductors and adductors of the thighs and a positive Kernig's sign. There was no nuchal rigidity, skin rash, lymphadenopathy, palpable liver and spleen or neurologic abnormality.

Laboratory work-up showed repeatedly normal hemograms. The white blood cell counts varied between 6,900 to 11,000 cells per cu. mm. Urinalyses showed specific gravity between 1.008 and 1.018, persistent 1 to 2+ albuminuria and some hyaline and finely granular casts; they were otherwise negative. Spinal fluid examination on admission showed six cells, positive Pandy test, 23 mg. per cent protein, 75 mg. per cent sugar and 660 mg. per cent chlorides. Four days later the spinal fluid revealed 230 cells with 86 per cent lymphocytes, negative Pandy reaction, 34 mg. per cent protein, 54 mg. per cent sugar and 680 mg. per cent chlorides. Culture of both spinal fluids was negative. Blood Kahn was negative. Blood urea nitrogen on the ninth day of illness was 16 mg. per cent.

The course for the first four days following

admission was marked by irregular high fever with diurnal elevations up to 103.5°F. (via rectum) prostration of moderate degree, drowsiness, headache and severe pain, tenderness and voluntary spasm of the limb, back and neck muscles. On the sixth day of illness, the first day of normal temperature, icteric sclerae and bile in the urine suddenly developed. The icterus index was 21. Neither the liver nor spleen became palpable. By the ninth day of illness the muscle pains and tenderness had subsided completely. On the thirteenth day the icterus index was 12; no leptospira were seen in the patient's urine. On the thirty-first day the icterus index was 5 and the cephalin flocculation test was negative. The patient was discharged on the fortieth day of illness, having been asymptomatic for about one month except for transient episodes of back pain.

The agglutination studies were as follows:

	9/25	10/11	10/16
L. canicola	1:1,000	1:1,000	1:10,000
L. icterohaemorrhagiae . .	1:100	1:100	1:100

CASE II. J. H., a thirty-three year old colored male window cleaner, was admitted to the isolation service of Gallinger Municipal Hospital on November 2, 1948, with the chief complaints of joint pains, fever and chills for one day. The patient had been well until two days before admission at which time he became aware of an ache in the region of the left scapula. The next day he became acutely ill with constant dull pain in both scapulas, shoulders, mid-back, hips and knees aggravated by any movement; severe frontal headache; fever; sweats; and a shaking chill. On the day of admission in addition to the preceding symptoms there were anorexia, sore throat, vomiting and several chills. He sought medical attention and was given 300,000 U. of penicillin in oil and wax after moderately severe pharyngitis was discovered. Because there was no improvement he presented himself that evening for hospitalization. Marked drowsiness and stiff neck were now obvious and the patient was admitted as a meningitis suspect.

On weekends for the past five years the patient had worked for a veterinarian who cared for cats and dogs only; about nine days before

admission he received a minor dog bite on the right hand, which healed without incident.

Physical examination revealed a well developed, well nourished adult colored male, acutely ill and prostrated. Striking were drowsiness and lethargy. His rectal temperature was 102.4°F., pulse 130, respirations 22 and blood pressure 80/60 (both arms). Significant findings were photophobia; markedly injected conjunctivae; a hemorrhage of pin-head size in the lateral aspect of the left lower palpebral conjunctiva; 4+ nuchal rigidity; tender neck muscles; 1+ pharyngeal injection; tender, small, shotty anterior and posterior cervical adenopathy; small, discrete, non-tender axillary and inguinal adenopathy; positive Kernig's and neck Brudzinski's signs; tender arm and calf muscles; several petechiae on the right lower leg and right forearm; several small purpuric lesions on both ankles and legs and on the right forearm; and a small splinter hemorrhage under the right little fingernail. There was no icterus, palpable liver or spleen.

Laboratory findings included normal hemoglobin and red blood cell count. White blood cell count on admission was 14,500 per cu. mm., with a differential count of 30 per cent polymorphonuclear cells, 43 per cent band forms, 7 per cent myelocytes, 15 per cent lymphocytes, 5 per cent monocytes and no eosinophils. On the sixth and ninth days of illness the white blood cell count was 10,650 and 8,000 per cu. mm., respectively. Urinalysis on admission showed a specific gravity of 1.015, no albumin or bile or sugar, numerous hyaline and finely granular casts, four to five red blood cells per high power field and ten to fifteen white blood cells per high power field. Subsequent urinalyses showed a return to normal by the ninth day of illness except for one on the sixth day which contained 2+ albumin and ten to fifteen red blood cells per high power field. The spinal fluid on admission was clear and colorless, exerted a pressure of 90 mm. of fluid and contained six lymphocytes, 35 mg. per cent protein and reduced Benedict's solution in three of five test tubes. Colloidal gold reaction was negative in all tubes. Culture was sterile. Blood Kahn was negative. Multiple agglutination studies and malarial smears were negative on two occasions. Blood cultures, three with and three without added penicillinase, taken on admission and during the next three days, were uniformly negative. On the sixth day of illness the bleeding time

was two minutes; coagulation time, three minutes; clot retraction, normal; Rumpel-Leede test, negative; prothrombin time, thirteen seconds (100 per cent); and icterus index, 10. Platelet counts on the sixth, seventh and seventeenth days of illness were 163,400; 172,860 and 520,000 per cu. mm., respectively. Total serum protein was 7.6 gm. per cent, serum albumin 5.2 gm. per cent and serum globulin 2.4 gm. per cent. Three tests of liver function during the acute phase of the disease and during convalescence were as follows:

	11/5	11/12	11/23	11/30	12/7	12/14	2/6
Bromsulphalein retention		1%			8%	6%	5%
Thymol turbidity	5.6 U.	5.4 U.	8.4 U.	9.2 U.	11.6 U.	9.4 U.	6.4 U.
Cephalin flocculation ..	3+	4+	3+	4+	4+	4+	2+

The patient was believed to have acute meningococcemia and was treated with sulfonamide N U 445, 6 gm. intravenously immediately and 1 gm. orally every four hours. This was continued for fourteen days. The possibility of canicola fever was considered and blood serum was sent to the National Institute of Health for agglutination studies. The patient's temperature fell precipitously the night of admission and stayed normal for about thirty-six hours when it rose abruptly to 103°F. and then gradually fell by lysis during the next six days. From the eleventh day of illness until discharge his temperature remained normal. On the fifth day of illness the meningeal signs, myalgia and arthralgia subsided. On the sixth day the petechiae, purpuric lesions and photophobia disappeared, but on that day herpes labialis developed and became hemorrhagic and crusted in six hours. On the seventh day the persistent frontal headaches were thought to be explained by the finding of acute right ethmoiditis and right tubotympanitis, which was probably superimposed on a chronic sinusitis. Appropriate treatment resolved the headache by the tenth day. The patient was asymptomatic from the eleventh day until discharge, the seventeenth day of illness.

Agglutination studies were as follows:

	11/3	11/10	11/23	12/7	12/20	2/6
L. canicola	neg.	1:100	1:10,000	1:100,000	1:100,000	1:100,000
L. icterohaemorrhagiae	neg.	1:100	1:100	1:10,000	1:10,000	1:100

Follow-up of this patient revealed a prolonged symptomatic convalescence. On November 23, 1948, the patient had nosebleeds and weakness; November 30th, weakness and backpains and tender back muscles; December 7th, backpains; December 14th, backpains and neckpains; and February 6, 1949, backpains considerably reduced but back muscles still tender.

Comments. In Case I it was impossible to ascribe the source of infection to the patient's dog for he may well have contracted the disease from swimming or while at work. The characteristic signs and symptoms were present, namely, fever, headache, prostration, myalgia with tender muscles, sore throat, bradycardia, photophobia, injected conjunctivae and drowsiness. However, to complicate the picture there was a history of lower extremity weakness but without definite objective findings of muscle paresis, and a lymphocytic pleocytosis. A diagnosis of poliomyelitis had to be considered strongly; and if the course had remained unchanged, the final diagnosis might have been non-paralytic poliomyelitis. But at this time mild jaundice was discovered and led to the correct diagnosis. Mention should be made of several interesting points in this case: the lack of leukocytosis; the lack of gastrointestinal, renal and bleeding manifestations; the normal spinal fluid initially; the lymphocytic pleocytosis of 230 cells in the absence of meningeal signs; the mild icterus for six days unassociated with a palpable liver or spleen; the diagnostic agglutination titer as early as the eighth day of illness; and the rapid, uncomplicated convalescence.

In Case II the source of infection most probably was one of the dogs at the veterinarian's clinic. Many would doubt that the dog bite itself was the mode of entrance of the leptospira into the body unless the wound was contaminated with urine. However, a case recently reported was suspected of having been transmitted by a dog bite.⁸⁶ The course was typical with sudden onset, fever, chills, headache, vomiting, sore throat, arthralgia and myalgia with tender muscles, injected conjunctivae, hypotension, drowsiness, photophobia and on the second day marked meningeal signs. The confusing issue in this case was the finding of petechiae and purpuric lesions. These in combination with the sudden onset of fever, repeated chills and prostration made the treatment for meningococcemia imperative. This is the first case in which such skin lesions have been reported. The marked shift

of the granular white blood cells to the left is not at all unusual. It is interesting that microscopic hematuria was observed on the same day that a hemorrhagic herpes labialis appeared. The chances are that the normal temperature for thirty-six hours after the injection of penicillin is attributable to the antibiotic. There is no evidence that the sulfonamide influenced the course of this patient's illness. The agglutination titers of the second test illustrate what sometimes happens early in the course of leptospiral infections. This patient's convalescence is more typical of the usual type of recovery than that experienced by the first patient. It is noteworthy that although there was no jaundice or liver enlargement or tenderness, liver function studies would seem to indicate an active intrahepatic pathologic process, in all likelihood a mild anicteric leptospiral hepatitis.

SUMMARY

1. Those aspects of canine leptospirosis of importance to an understanding of canicola fever are discussed. The public health significance of the canine infection is stressed.

2. The properties of the organism are described.

3. The literature on canicola fever is reviewed, with special emphasis on methods for early diagnosis of the disease.

4. Two new cases of canicola fever are described and discussed.

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Seminars on Arteriosclerosis

Pathology of Atherosclerosis*

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ANY consideration of the problem of atherosclerosis must necessarily take its departure from an understanding of the morphology of the disease and, indeed, the validity of pathogenetic theories must finally be judged by reference to morphologic criteria. For these reasons we have chosen to review at some length the characteristic morphologic features of atherosclerosis before proceeding to a general consideration of its genesis.

The word "atherosclerosis" is not capable of definition except in descriptive morphologic terms, since knowledge, which may in the future permit a clinical or etiologic definition, is still inchoate. Atherosclerosis denotes a pathologic change affecting the intima of arteries that is characterized by focal thickenings of the intima in which stainable lipids can readily be demonstrated in and between the cellular elements. The larger lesions show, at the one extreme, an almost exclusively fibrous composition with only minimal quantities of lipid material while, at the other extreme, they contain lipid accumulations of massive proportions with extensive necrosis of the central parts of the lesions commonly culminating in disruption of the intimal lining. The characteristic lesions are highly variable and may present all gradations between these two extremes. Lesions of any composition may show more or less extensive calcification. The term "atheroma" refers to an atherosclerotic lesion of which the centre is necrotic and occupied by a grumous mixture of lipid material and tissue debris.

MORPHOLOGY OF ATHEROSCLEROSIS

While opinion has not been unanimous in the past,^{67,103,105} it is now generally accepted that the so-called fatty flecks or streaks of arteries are the early lesions of atherosclerosis and that they may develop into the more advanced lesions of the disease^{3,141,145} although, on the other hand,

they may retrogress. These earliest lesions are commonly seen in the intima of the aorta in childhood or adolescence. The smallest that are readily visible to the naked eye appear as minute round or oval yellow spots that project slightly above the intimal surface. A number of these spots may be arranged in rows and commonly coalesce to form streaks orientated along the longitudinal axis of the aorta. The fatty flecks or streaks usually are distributed along the posterior wall of the thoracic aorta lying between and around the orifices of the intercostal arteries rather than immediately at their mouths, although more advanced lesions eventually spread to involve them.

It is important to recognize that fatty flecks and streaks are not limited to childhood, nor to the aorta, but may occur at any age in any artery.^{103,115,141} Hence the intimal tissue in which they occur may differ because of age changes or because of the differing structure of different arteries. The precise form of the lesions may be modified by these circumstances.

While some of the fatty flecks or streaks undoubtedly retrogress leaving either a grossly normal intima or minute fibrous plaques devoid of lipids,^{19,33,67,75} others show a progressive accumulation of lipids and the development of connective tissue caps that cover them smoothly. The larger the accumulation of lipids and the greater the total thickness of the plaque the less likely is the possibility of complete removal of the lipid material in a retrogressive phase. However, pearly-grey lenticular lesions up to moderate size may be found that are almost free of fat or even purely fibrous in composition. The larger collections of lipid material, covered by a fibrous cap, tend to remain and the central area of maximum lipid concentration becomes necrotic, forming an atheromatous lesion. The rich lipid content of such atheromas is indicated by a more or less conspicuous yellow colour

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shining through the grey translucent fibrous covering. At this stage the intima may be greatly thickened by lesions that bulge into the lumen.

It appears that smaller atheromatous lesions of predominantly fibrous composition may remain virtually static, but the central areas of necrosis in the larger lesions tend to spread in all directions with a corresponding enlargement of the central pool of lipids. Extension of necrosis toward the intimal surface ends with disruption of the lining membrane. In this event much of the grumous content of the atheroma may be discharged into the blood stream and the ragged defect becomes covered by thrombus material. Necrosis may also extend deeply into the subjacent media as well as in lateral directions.

Adjacent atherosclerotic plaques tend to coalesce and lesions in various stages of development may be present in juxtaposition. A fresh peripheral extension of older lesions is often indicated by the development of a bright yellow marginal zone of superficial lipid accumulation.^{78,138} Inspection of the intimal surface and cut edge of an artery usually discloses a uniformity in the character of the lesions during the first two or three decades of life. Thereafter the morphologic variations increase in complexity until in old age the full gamut of pleomorphism is expressed. It is occasionally noted that a large number of rather similar plaques may be superimposed upon an intima that is characterized by the usual variable atherosclerotic lesions but, nevertheless, pleomorphism remains a characteristic feature of the later stages of the disease.

Microscopic examination of early fatty streaks discloses swelling and increase of the intimal metachromatic ground substance in which fine droplets of sudanophile lipid material are scattered; the subjacent elastic lamellae also may be mantled with minute droplets of lipid. Intracellular accumulations are found in lipid-filled globular macrophages ("foam cells") and in spindle-shaped or stellate mesenchymal cells in the intima. The latter are best seen in sections cut parallel to the intimal surface. The lining endothelial cells seldom contain any stainable lipid material.

As the lesions advance fibrous proliferation becomes more prominent in their superficial layers while there is a concentration of lipid-filled foam cells in their deeper parts. The fibrous

cap thus formed over the main lipid accumulation exhibits excess quantities of metachromatic ground substance,^{17,42} varying degrees of hyalinization and sometimes fibrinoid necrosis.^{62,111} Many of the deeply placed foam cells disintegrate and a pultaceous mass of lipids and necrotic debris is formed. In this atheromatous pocket numerous crystals of cholesterol are precipitated. The internal elastic membrane, encroached upon by the necrotic atheromatous area, exhibits fraying and fragmentation, sometimes with frank rupture and invasion of the media by the atheromatous process. The lateral margins of the central necrotic zone are usually formed by masses of lipid-filled macrophages among which are a few stellate fibroblastic cells and scattered lymphocytes. These areas in turn merge at the edges of the lesion with the investing fibrous layer. The latter may also contain finely dispersed extracellular lipid accumulations particularly in its hyalinized portions.

Aorta. The aorta is the vessel in which atherosclerosis attains its earliest and most extensive expression. It is the vessel in which atherosclerosis is most readily observed and in which the process has been most extensively studied. Lesions are occasionally observed in the aortas of stillborn or newborn infants.⁶⁹ Before the age of twenty the disease occurs predominantly in the form of fatty flecks and streaks, most abundant in the thoracic part of the aorta. In 302 subjects under the age of sixteen Zinslerling¹⁴⁵ found the incidence of such lesions to be 95.4 per cent, while Albert³ found fatty intimal lesions in an incidence of 86.3 per cent among 131 subjects ranging from four months to fifteen years of age. The latter investigator encountered not a single completely normal aorta from the eighth year upward. The lesions increase not only in incidence but also in severity with increasing age. The earliest fatty flecks are seen in the ascending limb of the arch, but with increasing development of the disease the lesions extend distally in progressive fashion. In subjects over the age of twenty years it is exceptional to find an aorta that is completely normal, even to cursory inspection.

Data dealing with the incidence of atherosclerosis in the older age groups are clearly based on much less rigid criteria. The incidence of the disease is said to vary from about 50 to 90 per cent in the sixth decade and to reach an incidence of 100 per cent only in the eighth decade.^{91,114,139} It is striking, however, to ob-

serve on occasion how slight may be the development of atherosclerosis of the aorta even in aged individuals. While the earliest lesions are located predominantly in the thoracic aorta, those that develop in the abdominal aorta tend eventually to overtake them and to surpass them in severity. Thus the lesions of advanced atherosclerosis of the aorta are most severe in its abdominal part. An outstanding exception is the occurrence of advanced atherosclerosis of the thoracic aorta superimposed on the lesions of syphilitic aortitis, which often stands in contrast to the much lesser degree of atherosclerotic involvement of its abdominal portion.

Erosion of the intimal surface of the most advanced and coalescent atheromatous lesions, usually located in the abdominal aorta, is often followed by the development of small or large mural thrombi and sometimes by thrombotic occlusion of the abdominal aorta. Both mural thrombi and the extruded contents of ruptured atheromatous plaques may be the source of peripheral embolism.^{48,83,143} Extensive involvement of the media by confluent atheromatous lesions of the abdominal aorta may lead to the development of aneurysms which may leak or rupture.

Coronary Arteries. The intima of the coronary arteries is normally thicker than that of other vessels and its thickness increases with age. There is a wide variation in the thickness of the intima during childhood and adolescence and it may occasionally even exceed that of the media. In later life the intima frequently is thicker than the media. The thickening is concentric and rather uniform and is composed of fibrous tissue and elastic fibers.^{40,56,140} Somewhat similar but eccentric thickenings of the intima have been described in the coronary arteries of newborn infants.^{29,44,85,144} Dock²⁹ found that these plaques are about two and one-half times thicker in male than in female infants. Zinck¹⁴⁴ found that they occurred only at points of arterial branching and suggested that they are concerned with the control of blood flow. Dock, however, thought that the thickenings he described were developmental irregularities that favored the subsequent development of atherosclerosis in these areas and that perhaps accounted in part for the higher incidence of severe coronary atherosclerosis in males. The demonstration of stainable fat in such fibrous plaques led Fangman and Hellwig⁴⁴ to conclude

that they were, in fact, early atherosclerotic lesions.

Atherosclerosis of the coronary arteries begins, as elsewhere, as fatty flecks and streaks. However, they always appear later than those of the aorta. The lesions occur in a slightly lesser incidence and degree of severity in the coronary arteries than in the aorta^{114,139} but it is not uncommon to see severe atherosclerosis of the coronary arteries in the presence of a relatively slight degree of aortic disease. In the first decade only the occasional minute lesion is seen in the intima of the coronary arteries. During the second and third decades they elongate, enlarge and progress to form definite atherosclerotic plaques. The process begins first toward the origin of the coronary arteries, spreads distally and finally involves the fine epicardial branches although it does not extend to those that penetrate the myocardium. The alterations begin earlier and are more marked in the left coronary artery,^{40,114,141} particularly in its anterior descending branch. The lesions are more prominent on the surface of the vessel nearest the heart muscle;^{14,141} but when the artery actually lies below a bridge of myocardium for part of its course, the buried portion is less subject to the disease.⁵¹

Advanced lesions cause extensive and irregular thickening of the intima, marked stenosis of the lumen and atrophic thinning of the media. The lesions frequently involve the greater part of the extramyocardial coronary circulation, but isolated nodular, stenotic intimal plaques are seen on occasion.⁵

The lesions may progress or retrogress in much the same manner as those found in the aorta. They frequently contain dystrophic calcium deposits. The atheromas of the coronary arteries, more than those found in any other vessels, are subject to secondary vascularization.^{71,92} Paterson has demonstrated that these minute vascular channels may rupture and cause a haemorrhage into an atheroma with the formation of a hematoma and consequent distortion of the plaque. This may cause occlusion of the artery of itself^{59,130} or precipitate thrombus formation.^{59,88,93,96} Analogous phenomena occur in vessels other than the coronary arteries but are uncommon.^{94,95,131} Extension of necrosis in the plaque to the intimal surface may cause its disruption. Extrusion of the contents of the atheroma with resulting embolism distally is probably more common than has been sus-

pected previously.^{15,130,143} Thrombosis and extreme stenosis of atherosclerotic coronary arteries is, of course, very frequent.^{59,110}

Cerebral Arteries. The anatomic peculiarities and age changes occurring in the cerebral arteries are detailed in the studies of Wolkoff,¹⁴² of Baker¹² and of Carmichael.²⁴ The work of Wolkoff stands strangely alone as the only comprehensive study of the atherosclerotic lesions of these vessels.

Atherosclerosis affects the cerebral arteries much later in life than the aorta or coronary arteries. Atherosclerosis of the arteries of the base of the brain is seldom seen in subjects less than thirty years old, and lesions in the arteries of the basal ganglia are rare before the age of fifty. The lesions are preceded in incidence by those of the aorta, the coronary arteries and the large branch arteries arising from the aorta.

The microscopic morphology of the lesions is similar in general to that observed in atherosclerotic plaques in the aorta or coronary arteries. However, we have observed a striking variation in the morphology of atherosclerosis as it affects the cerebral arteries that has not been much emphasized by those who have previously described it.^{24,142} The internal elastic membrane deep to some of the atheromatous lesions may show a clearly defined gap through which the lipid content of the atheroma is continuous with a large pool of similar lipid in the media. The media in such areas is destroyed, sometimes to the extent of its full thickness. An advanced lesion may have a shape somewhat like an hour glass, containing as much lipid in its medial as in its intimal part. According to Wolkoff¹⁴² the smaller intracerebral arteries or arterioles may show diffuse deposits of extracellular lipid in the intima.

Among the sequelae of atherosclerosis of the cerebral arteries are thrombosis and the development of aneurysms particularly of the basilar artery.

Arteries of the Abdominal Organs. The arteries of the abdominal organs develop atherosclerotic lesions similar to those found in other arteries.^{18,45,80,120} Their incidence is moderate, their onset relatively late and their degree of severity is usually slight or intermediate. The lesions tend to be more numerous and prominent near the origin of the large branches of the aorta and decrease in their smaller ramifications. It has been observed that there is a tendency for plaques to be located at those points where an

elongated, tortuous splenic artery bends and the flowing blood impinges on the intima. It has been our experience that while this observation is true, it accounts for the localization of only a minority of the lesions. Occasionally, advanced lesions in abdominal arteries may cause extreme stenosis of the arterial lumen, may precipitate the formation of an occlusive thrombus, may become eroded and give rise to emboli, or may lead to the formation of an atherosclerotic aneurysm, but such complications are uncommon.

Arteries of the Extremities. The atherosclerotic lesions of the peripheral arteries usually consist predominantly of fibrous tissue and contain only small amounts of finely divided extracellular lipids at the time they are examined.^{13,107,108} Lesions rich in intracellular and extracellular lipids and true atheromas occur not infrequently, however,^{13,89} and they have been observed to be particularly common in the arteries of patients dying with diabetes mellitus.¹²⁹ The lesions are more prominent toward the origins of the arteries and are less marked in the distal segments. The arteries of the legs are especially prone to the disease. The intima is irregularly thickened by the process and occasionally lesions may be vascularized in the same manner as atheromas in the coronary arteries. Calcification of the intimal lesions may occur. Extreme stenosis of the arterial lumen may be caused either by plaques that contain large quantities of lipids or that are predominantly fibrous at the time of observation. Thrombosis is a complication and it may be very extensive in the stenosed vessels of a limb undergoing ischemic necrosis. Atherosclerotic aneurysms are rare except in the common iliac and popliteal arteries.

Pulmonary Arteries. The incidence of atherosclerosis of the pulmonary arteries is uncertain. Because of differing criteria the figures of incidence given in the literature are variable. Some studies^{84,86} place the incidence of grossly visible lesions at 6 to 8 per cent while others^{20,115} place the incidence of changes as high as 65 or 70 per cent.

Atherosclerosis of pulmonary arteries does not differ qualitatively from that seen in the aorta but is usually of a mild degree of severity. Calcification is seen uncommonly and only on microscopic examination. Ulceration of the intima appears to have been described by only one author.⁶⁰ The changes are least marked in the main stem of the pulmonary artery and its extra-

pulmonary branches. In this area the lesions are commonest above the cusps and may involve the commissures of the valve slightly. They increase in incidence and severity at the hilus of the lung and in the larger intrapulmonary branches, and usually diminish in the smaller ones. Some of the lesions are fibrotic but others, even in small elastic or muscular branches, contain lipid-laden foam cells and finely divided extracellular fat.

The lesions occur in all decades becoming more severe with increasing years. They are more common and severe in association with conditions thought to cause pulmonary hypertension.^{20,87} However, as many as one-fifth of all cases, particularly in the older age groups, with pulmonary atherosclerosis have no demonstrable interference with the lesser circulation, while about one-third of cases without sclerosis do show evidence of some interference with the circulation in the lungs.^{20,115}

Miscellaneous Observations. It may be remarked that certain vessels are seldom affected by atherosclerosis to any significant degree. Sappington^{107,108} has found that the fibrous intimal thickenings of the radial artery almost never contain accumulations of lipids. We have never seen an internal mammary artery in which atherosclerotic lesions were visible to the naked eye. Veins are subject to only minor atherosclerotic changes and these appear to be confined to the origin of the inferior vena cava.^{50,100} Reports of lesions resembling atherosclerosis that affect the major lymphatics are curious.^{63,90} The accumulation of lipids in tendons,²⁸ in the eye⁶⁸ and in mesenchymal tissues other than the vascular intima is common.⁴²

EXPERIMENTAL CHOLESTEROL ATHEROSCLEROSIS IN THE RABBIT

Before considering theories of the causation of atherosclerosis it is necessary to consider the morphology of experimental cholesterol atherosclerosis in the rabbit. The results obtained from feeding cholesterol to rabbits have had so profound an influence on our modern conception of human atherosclerosis that it is idle to consider any theoretic discussion of the human disease without first treating with experimental lesions. Several useful studies and reviews of experimental cholesterol atherosclerosis have been published.^{7,10,31,32,71} The great bulk of such work has utilized the rabbit as an experimental animal but there is a growing volume of litera-

ture concerning experimental cholesterol atherosclerosis in other animals such as chickens, dogs, hamsters and guinea pigs.

It has been found that if the diet of the rabbit is supplemented with $\frac{1}{2}$ to 1 gm. of cholesterol per day for three months or more, the animal will acquire arterial lesions resembling those of human atherosclerosis. The cholesterol may be fed in naturally occurring forms such as egg-yolks or cream, or it may be fed as a purified substance dissolved in oil or mixed with the food as a powder. It may even be administered intravenously as a colloidal solution. In general, the larger the amount of cholesterol that is administered the more extensive will be the resulting lesions. Grossly visible lesions are seldom seen before the end of about six weeks of feeding of cholesterol, and prominent lesions require three to six months for their development. The experimental regimen induces a state of hypercholesteremia and hyperlipemia the onset of which precedes that of the arterial lesions. Cholesterol and other lipids accumulate in large amounts not only in the arterial intima but also in the cells of the reticulo-endothelial system, mesenchymal tissue and the cells of such parenchymatous organs as the liver and the adrenal glands.

In the aorta of the rabbit the gross lesions appear first as minute slightly raised round or oval yellow-white specks that shine through its intimal surface. The first area to be affected is just distal to the aortic ring and about the vessels arising from the arch. The lesions increase in size, become more sharply demarcated and circumscribed, and may attain a size of 1 or 2 mm. At the same time new lesions appear in the thoracic aorta and show some tendency to localize on the posterior wall about and between the ostia of the intercostal arteries. Such localization, however, is not strictly maintained. As the lesions progress there is a tendency to confluence so that large plaques and longitudinally orientated streaks develop and the intima becomes thick, rough and nodular. The lesions finally extend to below the level of the renal arteries or even toward the bifurcation of the aorta and into the peripheral vessels. The distal lesions, however, are always less severe than the proximal lesions. In advanced conditions the vessel may be subject to irregular dilatation and even aneurysm formation.

If the experimental procedure is stopped but the animal is allowed to live for periods up to

about three years, there occurs a partial resorption of the atheromatous areas with fibrosis and calcification. There is an accompanying loss of vascular elasticity.

Microscopically, intimal changes in the aorta may be detected as much as a month before grossly visible lesions are found. The subendothelial ground substance becomes slightly swollen and metachromatic and is seen to contain fine droplets of fatty material both in the extracellular ground substance and in lipid-filled histiocytes. Minute droplets of fat may be seen in endothelial cells. Branching, stellate cells of mesenchymal or fibroblastic type appear later and may be seen to be laden with lipid. As the lesions progress the foam cells of the deepest layers next to the internal elastic lamina enlarge in size and eventually undergo necrosis. Release of their lipid content results in the formation of atheromatous lesions. The superficial layer often shows a multiplication of several layers of fibrocytic cells, but this zone contains little collagen unless the lesion is allowed to mature for several months. However, an extensive reticulum forms among the foam cells of the plaques. The lesions may become confluent and form an irregular diffuse intimal thickening that may involve almost the whole surface of the aorta and that may average one, two or even more times the thickness of the media.

The underlying elastic laminae may show degenerative changes and new fine fibrillar elastic fibres may be formed or the media may be invaded by the process with the accumulation of extracellular lipids and foam cells. There are degenerative fatty changes in the neighboring muscle fibres. A further medial lesion consisting of a focal necrosis in the inner third of the media that contains a small amount of extracellular lipid may be seen occasionally. The location of such medial lesions may be quite independent of any intimal alteration.

Vascularization of the intimal plaques is not a feature. Migration of endothelial cells from the intimal surface and of muscle cells from the media into rather advanced lesions has been described by Altschul.⁷ We have described the occurrence of mitotic figures in the foam cells and fibrocytic elements in the intimal plaques of the aorta.⁸¹

If the lesions are allowed to retrogress after the cessation of cholesterol feeding, a partial resorption of the extracellular and intracellular

lipid content of the area occurs. In small lesions this resorption may be complete but in larger lesions an atheromatous pool of pultaceous and crystalline lipid material remains surrounded by phagocytes and lymphocytes and covered over by fibrous tissue. Calcification and the formation of new elastic fibrils are common occurrences in such regressing lesions.

The changes described above are not confined to the aorta. They occur regularly in the coronary and pulmonary arteries and in small arteries elsewhere excepting those of the kidney and brain. Altschul⁶ has succeeded in producing atherosclerotic lesions of the cerebral vessels by a modification of the feeding procedure.

There are similarities and dissimilarities between human atherosclerosis and experimental cholesterol atherosclerosis as described in the rabbit.^{7,10,31,32,72,74} The most obvious difference lies in the fact that the appearance of the experimental arterial lesions is preceded by a more or less conspicuous accumulation of lipids, rich in cholesterol, in the cells of the reticulo-endothelial system and of parenchymatous organs.⁷ No such lipid accumulations are found in association with, much less preceding, the development of ordinary human atherosclerosis. The second gross difference is apparent in the distribution of the arterial lesions. In the rabbit these are found in the aorta, its major and secondary branch arteries and in the pulmonary arteries. The cerebral vessels are exempt, except under special circumstances,^{6,102} and the retinal artery is not involved. Moreover, the most severely affected area is the thoracic aorta. In man, while the aorta and its branches are the main site of the disease, atherosclerosis reaches its maximum development in the abdominal portion of the aorta. The pulmonary arteries are affected to a minor extent only and the cerebral and retinal vessels are frequently the sites of lesions.

On the other hand, the individual arterial lesions of the human and experimental diseases present striking similarities both grossly and microscopically. It is probable that if the experimental conditions that elicit the lesions in the rabbit were less forced, the experimental lesions would resemble the human disease even more closely. The tendency of the experimental and human lesions to localize along the posterior wall of the aorta and about points of branching is also worthy of note and the mature and re-

gressing lesions are quite similar to those in man, both grossly and microscopically.

Evaluation of the degree of equivalence of human and experimental atherosclerosis depends upon personal judgment which is influenced by training and experience. There are those who hold that none of the differences observed between the human and experimental lesion is of an essential nature¹⁰ and who maintain that an absolute identity between the natural and experimental lesion is too exacting a requirement.⁷⁴ We are inclined to emphasize that, while the morphologic similarities are so great as to suggest that one or more factors are common to the pathogenesis of both the human and experimental diseases, there are many points of difference that indicate either a divergence of pathogenetic mechanisms or the operation of different pathogenetic factors in the two diseases. Accordingly, great caution should be exercised in transposing interpretations derived from studies of experimental cholesterol atherosclerosis into terms supposedly applicable to the human disease.

ETIOLOGY AND PATHOGENESIS OF ATHEROSCLEROSIS

From a perusal of the older literature it may be observed how various concepts of the pathogenesis of atherosclerosis have arisen to popularity and have then given place to others. In each case the dominance of one concept appears to have led not merely to relegation of the previous one to an inferior position, but practically to its elimination from further consideration. At one time it was considered, for example, that atherosclerosis was fundamentally a mild chronic inflammatory process. This concept is no longer entertained although it is apparent that in certain cases, as for example in syphilitic aortitis, inflammatory processes contribute much to the development of the atherosclerotic process. It has been held that the physicochemical changes inherent in the aging of extracellular colloids in the arterial intima provided the fundamental alteration that led to the accumulation of lipids and thus to the development of atherosclerosis. The dominance of this theory over that relating to inflammatory processes has in turn been superseded by the view that chemical and physicochemical aberrations of the serum lipids and lipoproteins are fundamental to the pathogenesis of the lesions.

So popular has this view become that the casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the substrate of the vessel wall that it may occur in the absence of the blood vessels themselves. Still more recently there has been a tendency to turn toward a consideration of the importance of the metabolic activities of the arterial intima at the sites where atherosclerosis develops. It is too soon as yet to say whether these newer enthusiasms will cause the disappearance *in limbo patrum* of current concepts relating to the importance of deviations in the serum lipids.

A dispassionate view of the subject will disclose that there is something of truth in each of the major hypotheses of pathogenesis that have been proposed. These theories, if we may so designate them, are not mutually exclusive but may be regarded as complementary. At present they do not provide a satisfactory explanation of all the factual data available concerning atherosclerosis, but each contributes something to our understanding of the condition.

Lipids in Relation to Atherosclerosis. The fatty character and cholesterol content of the lesions of atherosclerosis have been well recognized since the time of Virchow but it was not until the early years of the present century that interest in the precise composition of the fatty content of the lesions led to the first crude chemical analyses of the various lipid fractions. This work received a further stimulus when experimental atherosclerosis was successfully produced by feeding cholesterol to rabbits, and great interest was evoked by the demonstration that cholesterol and its esters were the major components of the atherosclerotic lesions, both in man and in experimental animals.

More precise chemical knowledge of human and experimental atherosclerotic lesions has become available during the last two or three decades^{22,23,77,132,133} and it has become apparent that their lipid composition is very complex. Such studies have shown that atherosclerotic lesions contain lipids in amounts far greater than that found in the normal intima and in quantities that increase *pari passu* with the increasing severity of the lesions as judged by gross or microscopic inspection. Cholesterol and its esters have been shown to make up about half of the lipids present in the earlier lesions and 60 to 70 per cent of the lipids in the more advanced lesions. The remainder of the fatty

material is largely composed of neutral fat and of lecithin and sphingomyelin.

The quantity of lipids that accumulates in the atherosclerotic lesions is so large as to preclude the possibility that they originate from the simple breakdown of tissue in the intima. It is evident, therefore, that the lipids originate elsewhere and are brought into the intima and deposited there. The various lipids in the atherosclerotic lesions are present in proportions that approximate¹³² but are not precisely the same²³ as those normally found in the serum. These findings have been construed as evidence of the origin of the deposited lipids from the blood plasma.

The early interest in cholesterol was intensified further by the observation that a state of hypercholesterolemia preceded and accompanied the development of experimental atherosclerosis in the rabbit. Indeed, it soon became apparent that hypercholesterolemia of some degree was a *sine qua non* for the production of these lesions. The normal level of cholesterol in the rabbit's serum is low relative to that in man which is about three times as high. Although the minimal effective degree of hypercholesterolemia has not been determined with accuracy, it appears that continuous elevation of the blood cholesterol in the rabbit approximately to the level that normally is found in man is sufficient for the eventual production of experimental atherosclerosis. Higher levels of hypercholesterolemia permit the more rapid development of the lesions; and if the hypercholesterolemia is induced by the intravenous administration of colloidal solutions of the substance, lesions may be produced within a few weeks.²⁶ It has been found that there is an association between the degree and duration of experimental hypercholesterolemia and the severity of the resulting atherosclerotic lesions. This association is irregular, however, and it is not possible to predict exactly the severity and extent of the atherosclerotic lesions that may result from a certain duration and degree of induced hypercholesterolemia.^{101,133}

The importance of hypercholesterolemia in relation to experimental atherosclerosis led to studies designed to establish a similar relationship in man. However, numerous investigations have failed to demonstrate that hypercholesterolemia is essential to the development of human atherosclerosis. Indeed, in the vast majority of cases with or without clinically demonstrable

atherosclerosis the blood cholesterol level is normal.⁸ Lande and Sperry⁷⁰ compared the total lipid content of the aorta at autopsy with the serum cholesterol of patients who had died suddenly, in most instances from trauma. No relationship was established. In the opinion of Peters and Van Slyke:⁹⁸ "No general disturbance of lipid metabolism has been demonstrated in patients with atherosclerosis."

Nevertheless studies of relatively small groups of patients who have suffered an occlusion of a coronary artery, often at a comparatively early age, have shown the frequent occurrence of a mild, spontaneous hypercholesterolemia in such selected patients.^{27,41,53,76,100,117} They apparently have also an abnormally advanced degree of atherosclerosis of the coronary arteries. It has long been appreciated that certain diseases such as diabetes mellitus, hypothyroidism and hypercholesterolemic xanthomatosis are often associated with hypercholesterolemia and enhancement of the atherosclerotic process. It would appear that the individuals referred to above, who suffer from spontaneous hypercholesterolemia and premature coronary occlusion, should be grouped with those suffering from hypercholesterolemia of other causes as examples of the promotion of atherosclerosis by abnormality of lipid metabolism, since they are not representative of the generality of atherosclerotic patients. Genetic studies¹ suggest that the metabolic abnormality observed among the cases of premature coronary atherosclerosis is an hereditary fault of lipid metabolism which is transmitted as a mendelian dominant.

Experimental cholesterol atherosclerosis has offered an admirable tool for the investigation of factors that might influence the degree of hypercholesterolemia and hence might affect the pathogenesis of atherosclerosis. The role of the thyroid has been studied by Turner and others, and it has been found that hypothyroidism produced by thyroidectomy¹²⁸ will promote hypercholesterolemia and the development of atherosclerosis due to the feeding of cholesterol to rabbits. Dogs treated with thiouracil and fed cholesterol also respond with the development of hypothyroidism, hypercholesterolemia and atherosclerosis although they are resistant to cholesterol feeding alone.¹¹⁸ The administration of inorganic and organic compounds of iodine or of thyroid extracts moderates the degree of hypercholesterolemia and the degree of atherosclerosis that follows cholesterol feed-

ing.^{21,82,104,124-127} These results are consistent with the observations in analogous conditions in man.

The effects of alloxan diabetes on the arterial system have been studied both in rabbits maintained on normal and on cholesterol-rich diets with findings that are the antithesis of experience with diabetes mellitus in man.^{35,79} Not only did alloxan diabetes not cause atherosclerosis in otherwise normal rabbits but it inhibited the expected development of atherosclerosis in rabbits fed cholesterol. Moreover, this inhibition occurred in spite of the fact that extremely high levels of hypercholesterolemia developed in some of the cholesterol-fed diabetic rabbits. It was found later that inhibition of the development of atherosclerosis was associated with a marked elevation of the serum phospholipids and neutral fat that occurred concomitantly with the rise of serum cholesterol.³⁸ On the other hand, if, as sometimes happened, the serum phospholipids and neutral fat were not markedly elevated in the presence of hypercholesterolemia, atherosclerosis would occur even in diabetic animals. It was also observed that if the diabetic state in cholesterol-fed rabbits were adequately treated with insulin, the expected inhibitory effect was abolished and atherosclerosis developed just as in normal rabbits fed cholesterol.³⁴ In these circumstances the ratios of the various lipids were found to be like those of cholesterol-fed non-diabetic animals.

Somewhat similar results were obtained by administering intravenously the detergents Tween 80 or Triton A20 to rabbits being fed cholesterol.^{64,97} Under these conditions a marked elevation of serum cholesterol was paralleled by an increase of phospholipids together with a moderate rise in the fatty acids of neutral fat. The development of atherosclerosis was strikingly inhibited. As in the case of the inhibition of the development of atherosclerosis in alloxan diabetes, certain animals developed lesions, and in these there was a very slight tendency for the phospholipid to cholesterol ratio to be decreased. Investigations in patients who had suffered occlusion of a coronary artery at an early age have shown that they often exhibit a decreased phospholipid to cholesterol ratio as do patients with a variety of diseases associated with hyperlipemia and excessive atherosclerosis.⁵² It should be noted that neither the alloxan diabetic state nor Tween 80 have any influence on

the retrogression of experimental cholesterol atherosclerosis.^{35,64}

These various observations have been interpreted to mean that an instability of cholesterol in the blood rather than the hypercholesterolemia *per se* is the general condition responsible for its deposition in the arterial walls from the plasma and, moreover, that the interrelations between the blood lipids are important factors in their stability. While the relation of the blood lipids to the plasma proteins are also of importance in this regard, particular emphasis has been placed upon the stabilizing role of the phospholipids, and Ahrens and Kunkel² have concluded from their studies in this field that "... a relationship appears to exist between the fixation of lipid in intimal cells and decreased phospholipid/cholesterol ratios."

A further advance in the knowledge of the physicochemical state of cholesterol in the serum has recently been made by Gofman and his associates⁵⁴ who have isolated from human and animal sera by ultracentrifugation macromolecular lipoprotein complexes of varying sizes and densities. Apart from those that occur in normal sera, these investigators have identified in addition abnormal cholesterol-containing compounds of low protein content and low density the occurrence of which they correlate with the development of atherosclerosis both in man and in cholesterol-fed rabbits. While these complexes are more common in hypercholesterolemic sera, they may occur also in the sera of patients with normal or even low levels of serum cholesterol. Moreover, they may be absent from hypercholesterolemic human sera. The presence of the abnormal giant molecules in association with severe atherosclerosis is almost invariable but they are lacking in a small percentage of such cases. Studies of the sera of apparently normal young adults revealed the presence of the abnormal giant molecules in a frequency approximating the expected incidence in later life of overt clinical manifestations of severe atherosclerosis. It has not been determined as yet whether the complexes isolated by Gofman et al. bear a direct causal relation to the development of atherosclerosis or whether they represent attendant effects that reflect some common cause. In any case it must be admitted that the association between the presence of these abnormal, giant molecules and the development of severe atherosclerosis is more exact and suggestive

than any other that has been demonstrated to date. However, such an association has not been shown to exist in the generality of individuals who develop only moderate degrees of atherosclerosis.

The effect upon the development of atherosclerosis of generalized systemic metabolic disturbances caused by overnutrition and undernutrition has received some attention. There is a considerable amount of clinical and pathologic data that tends to show that obese or overweight individuals are more prone to atherosclerosis and its consequences^{30,49,135} but this is not unanimously agreed.⁴³ On the other hand, it has also been observed that thin, undernourished persons tend to have somewhat less atherosclerosis than might be expected.^{11,136} Firstbrook⁴⁶ has recently advanced experimental data that purport to show that a lesser degree of atherosclerosis develops in undernourished rabbits during a course of cholesterol feeding than in the corresponding well nourished control animals. He contends that, in rabbits with similar initial weights, similar rates of weight gain and receiving cholesterol for the same length of time the extent of the lesions will be directly proportional to the average content of total cholesterol in the blood.⁴⁷ These conclusions are not convincingly established by the data but are of considerable interest; for if they should be substantiated, they may offer alternative explanations for some of the observations of experimental and human atherosclerosis and indeed may alter some fundamental concepts. In any case it seems probable that the nutritional state of the organisms has a relation to the pathogenesis of atherosclerosis but it is not known through what mechanism this factor exerts its influence. It may be noted in this connection that ordinary diets poor in fat and cholesterol, or rich in these substances, do not influence the cholesterol content of the blood in normal individuals.⁶⁵ On the other hand, diets completely free of cholesterol and fat will reduce the amount of cholesterol normally present in the blood.⁶⁵ A low-fat, low-cholesterol diet, while it has no effect in reducing the level of cholesterol in the blood, is capable of reducing the number of abnormal giant lipoprotein molecules when these are present in the serum.⁵⁴

Local Factors in the Arterial Wall. The problem of the localization of atherosclerotic lesions is a vexed one that lies at the center of any discussion of their pathogenesis. It is apparent that the

local, discrete distribution of atherosclerotic lesions depends primarily upon local differences in the arterial wall or upon local hemodynamic effects, since the composition of the plasma that bathes the vascular lining is essentially the same in all areas. The nature of these local differences is largely unknown but they may be divided into two groups of processes, those that tend to remove or mobilize lipids from the intima and those that tend to deposit or immobilize lipids in it. If the latter processes predominate over the former in a given region, an atherosclerotic lesion may develop at that site. On the other hand, if lipids are removed from the area as rapidly as they are brought to it, no lesion will form. The localization of atherosclerotic lesions is an expression of the relationship between these two opposing groups of dynamic processes. The amount and physicochemical state of the lipids in the blood plasma will affect this relationship secondarily and may determine whether an atherosclerotic lesion will occur or not, but such factors cannot influence its localization.

Experiments with animals fed cholesterol have shown that a variety of injuries or other modifications^{32,61} affecting the vessel walls, including sympathectomy,⁵⁸ will favour the localization of lipids in the affected areas and will accelerate the local development of atherosclerosis. On the other hand, the previous experimental or spontaneous deposition of plaques of calcium salts in the media has been shown to impede the deposition of lipids in the overlying intima while promoting it at their edges.^{32,57}

The occurrence of analogous phenomena in man is poorly documented. It has been suggested that mechanical or haemodynamic strain and trauma are responsible for the localization of atherosclerotic lesions in relation to the orifices of intercostal arteries, in relation to the points of vascular branching and in other areas. Perhaps the best evidence of a possible pathogenic role for strain and trauma is to be found in cases of localized or generalized hypertension for, while the data leave much to be desired, there remains little reasonable doubt that hypertension can aggravate atherosclerotic processes on occasion. The most clear cut example is the occurrence of atherosclerosis of the pulmonary arteries in association with pulmonary hypertension. The propensity of syphilis to enhance the development of atherosclerosis of the aorta is a good example of the effect of a vascular injury in man^{31,73} and, although the evidence is

not so distinct, it seems that other kinds of inflammation of the vessel wall may act similarly.^{4,5,66,106,113} Unfortunately, the experimental evidence that either hypertension^{9,28,134} or non-traumatic vascular inflammation^{16,112,121,122} influence experimental cholesterol atherosclerosis is not adequate.

These various observations on the localization and enhancement of human and experimental cholesterol atherosclerosis have been thought to depend principally upon increased or decreased rates of permeation of plasma through selected regions of the vessel wall. However, it is apparent that factors other than altered rates of permeation must operate to determine the continuing development of the succeeding atherosclerotic lesion. For many years it has been thought that the chromatropic ground substance and possibly altered collagen and elastic fibers of the intima may possess a special affinity for lipids that permeate the arterial walls. The cause of these antecedent intimal changes or even their character has never been clearly defined, and the nature of the supposed affinity between the altered intercellular elements of the intima and the plasma lipids has been expressed only in nebulous terms. Nevertheless, the concept continues to be a most attractive one and it is to be regretted that there is as yet no factual evidence to support it.

More recently attention has been turned to the relation between the intracellular metabolism of lipids in the arterial intima and the pathogenesis of atherosclerosis. While the mediation of a disturbed local metabolic activity in the genesis of atherosclerosis has been recognized and categorized by imponderable terms such as "anoxia" or "disturbed nutrition," great credit must be given to Leary⁷⁵ for emphasizing that normal as well as disturbed intimal metabolic processes may be important in the development of the lesions. He has maintained that there is a local metabolic defense mechanism which removes excess cholesterol from the arteries of young individuals and from the ascending part of the aorta at all ages. According to this part of his hypothesis cholesterol is transferred in the intima from wandering lipid-filled foam cells to fixed fibroblasts in which cholesterol esters are hydrolyzed and cholesterol is brought into solution in an excess of fatty acids. The solution of the cholesterol is said to permit the disappearance of the lesions and the restoration of the intima. This hypothesis may or may not be

correct but the principle upon which it is based is undoubtedly valid. In recent studies of the metabolism of cholesterol by the aorta it has been observed that it is not synthesized in the aortas of normal rats and mice.¹¹⁹ Preliminary studies in rabbits with experimental atherosclerosis have also indicated that the turnover of endogenous cholesterol is much faster in the normal parts of the aorta than in the adjacent atherosclerotic lesions.⁵⁵

It is probable that the macrophages or foam cells present in atherosclerotic lesions are similar to reticulo-endothelial cells elsewhere in the body and may be regarded as a part of that system. The foam cells have the appearance of macrophages elsewhere in the body and, like them, retain the ability to undergo mitosis.⁸¹ It has been observed that they avidly accumulate inert colloidal material in the same manner as the cells of the reticulo-endothelial system in general.^{36,99} This phenomenon occurs both *in vivo* and *in vitro*. We have also observed that large amounts of haemosiderin may be found not only in the general reticulo-endothelial system but localized in the plaques of experimental cholesterol atherosclerosis in rabbits within a few days after the intravenous injection of solutions of haemoglobin. It is apparent, therefore, that there are both morphologic and physiologic reasons for likening the foam cells of the lesions of experimental atherosclerosis to the recognized components of the reticulo-endothelial system.

In view of these relationships, observations such as those of Tompkins¹²³ become germane to the study of atherosclerosis. She injected colloidal solutions of cholesterol subcutaneously into mice and found that when the resulting acicular crystals of cholesterol came into contact with wandering macrophages they were converted into cholesterol esters at the cell surfaces. These entered into the cells and were segregated in the periphery of their cytoplasm as liquid crystal which gradually disappeared. It must be noted, however, that the rate of removal of lipids from experimental atherosclerotic lesions is incomparably slower than their disappearance from the reticulo-endothelial cells of organs such as the spleen after cholesterol feeding is stopped. Whether this fact expresses some fundamental cellular or metabolic difference or merely depends upon the fact that one group of cells is in the arterial intima and the other is in the spleen is not apparent.

There have been numerous attempts to inhibit or reverse the development of atherosclerosis by altering processes in the arterial wall. Experiments designed to dissolve deposited lipids as well as those planned to hasten their metabolic destruction have met with no success. Many such experiments have had no rational basis. Ethyl alcohol was one of the first substances to attract attention in this regard. During the last century it was thought that the use of alcoholic drinks promoted atherosclerosis but during this century an opposite view has gained ascendancy. Autopsy studies have failed to establish any effect of the habitual use of alcohol on the development of atherosclerosis,¹³⁷ while two studies of the effects of ethyl alcohol on experimental cholesterol atherosclerosis have produced contradictory conclusions.^{39,121}

Experiments employing the lipotropic agent choline have yielded equivocal results. It would appear that there is a slight inhibition of the development of experimental cholesterol atherosclerosis when cholesterol and choline supplements are administered together but this effect is apparent only within rather low limits of cholesterol dosage.^{37,116} Experiments in this laboratory have failed to confirm the claim that choline will affect appreciably the retrogression of experimental atherosclerosis.³⁷ Data derived from observations made on human subjects purporting to show that choline has an ameliorating effect on human atherosclerosis are unconvincing.

CONCLUSION

Our brief review of the morphology of atherosclerosis as it affects the aorta and the arteries of various regions of the body has brought out a number of morphologic features of the disease that demand pathogenetic explanation. The fact that atherosclerosis has its inception in childhood and is almost invariably present after adolescence at least in minimal degree indicates an inherent susceptibility of the human species to this disease. It is apparent that the lesions of atherosclerosis are capable of developing under conditions generally regarded as normal. In any event, no specific abnormality has been positively identified to explain the development of atherosclerosis in the generality of mankind. Indeed, most of the data bearing on the causation of the disease have reference to those cases of atherosclerosis of sufficient severity to bring about overt clinical manifesta-

tions. However, the segregation and study of cases of severe atherosclerosis may yet result in the formulation of principles applicable to all.

The fact that the lesions of atherosclerosis are characteristically patchy indicates the operation of local factors, since neighbouring and apparently identical areas of the intima may remain entirely normal. Further evidence of the influence of local factors on the pathogenesis of the lesions is provided by the observation that atherosclerotic lesions in certain arteries such as the aorta and coronary arteries are predominantly fatty in nature, while those in other vessels such as the arteries of the extremities are predominantly fibrous. There are ample morphologic grounds for regarding the atherosclerotic process as a dynamic one that may progress slowly or rapidly, may be episodic or continuous, may become static and may retrogress.

One of the most striking morphologic features of both human atherosclerosis and experimental cholesterol atherosclerosis is the great accumulation of cholesterol and other lipids in the arterial lesions. The quantity of lipid materials so greatly exceeds what could be conceived as originating from local tissue destruction that it has come to be generally accepted that the lipids infiltrate the intima from the blood plasma that bathes its surface. This process is usually accelerated in the presence of hypercholesterolemia but there are outstanding exceptions in observations of the experimental disease which make it apparent that instability of the solution of cholesterol in the blood rather than hypercholesterolemia *per se* is the general condition responsible for its deposition in the arterial intima. It is evident that the stability of cholesterol in the plasma is largely dependent on its relation to the plasma proteins and to the other blood lipids among which the phospholipids have been given special importance as stabilizing agents. It appears that an accelerated development of atherosclerosis is associated with diseases that are accompanied by demonstrable hypercholesterolemia. However, in the vast majority of cases of atherosclerosis hypercholesterolemia cannot be demonstrated and there is no general disturbance of lipid metabolism. The recent identification by the use of the analytic ultracentrifuge of giant lipoprotein molecules in the serum of certain patients and in cholesterol fed rabbits, and the correlation of their occurrence with the development of atherosclerosis has provided a more exact and

suggestive association than any other demonstrated heretofore.

While general conditions existing in the blood plasma may favour or prevent the deposit of lipids in the arterial intima, the local factors that operate in the vessel wall to determine the localization and to influence the subsequent development of individual atherosclerotic lesions are of equal importance. The nature and relative importance of various local factors have not been thoroughly investigated. However, suggestive evidence has been brought forward to implicate variations in permeability of the intima and possible variations in the affinity of altered intercellular ground substance and fibers for lipid substances. Certainly it is true that damage of any kind to the arterial wall predisposes the injured area to the subsequent development of atherosclerosis. Preliminary investigations strongly indicate the importance of the metabolic activities of the cellular elements in the intima in handling the lipids that are presented to them. There is evidence that the turnover of cholesterol is much slower in the aortic lesions of experimental cholesterol atherosclerosis than in the normal parts of the aorta. The study of local factors in the pathogenesis of atherosclerosis offers a fruitful field for further research.

Almost nothing is known of the means by which lipids enter the arterial intima or how they become fixed there. There is good reason to believe that they infiltrate the intima from the blood plasma but in what form they enter or by what mechanism they are transferred and how they are accumulated or removed is obscure.

The accumulation of lipids in the intima probably is the result of the preponderance of a group of general and local factors favouring the deposit and accumulation of lipids in the intima over another group of factors that favour their mobilization and removal. On the other hand, preponderance of the latter group of factors over the former would account for the diminution of lipid accumulations during periods of retrogression of the lesions. The clear recognition and understanding of all of the factors concerned in the etiology and pathogenesis of atherosclerosis must await the future.

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Clinico-pathologic Conference

Rheumatic Heart Disease with Acute Rheumatic Fever

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, B. R. (No. 192803), a white student seventeen years of age, was admitted to the Barnes Hospital on January 10, 1951, complaining of shortness of breath, palpitation and fatigue. The family history was irrelevant. Prior to the present illness the patient had enjoyed singularly good health. He had the usual childhood diseases without complications, and had a tonsillectomy at the age of six, but he denied any illness suggestive of rheumatic fever.

In February, 1948, while in robust health, the patient developed a cold and a sore throat; his temperature rose to 103 to 104°F. Two weeks after the onset of the respiratory infection he developed multiple painful joints. Although none of the joints was red or swollen, a number of them remained painful. The arthralgia was migratory in character. He was hospitalized in a rural institution where a diagnosis of rheumatic fever was made and salicylate therapy was prescribed. One month after the onset of the arthralgia firm, non-tender nodules appeared about the wrists and scalp. By April, 1948, the joint pains had largely subsided and the dose of salicylates was gradually reduced. As the patient became somewhat more active, however, moderate dyspnea appeared and he continued to have low grade fever averaging 100°F. for many months. Finally, in November, 1948, the patient's temperature returned to normal and the joint pains disappeared. Dyspnea likewise abated but the patient continued to feel weak. He gradually regained the feeling of well being and then returned to school.

In December, 1949, the patient again acquired a mild upper respiratory infection. Two weeks later he awakened with a "fluttering" feeling in the left chest and he was conscious of irregular, forceful heart beats. He was seen by a physician

who gave him penicillin and reinstituted salicylate therapy. Shortly thereafter the patient again noted dyspnea, arthralgia, fever up to 102°F. and subcutaneous nodules. He was kept in bed for six months, and gradually became symptom-free except for persistent fatigue. Because of lack of stamina he was unable to return to school. About one week before admission he was seen at an itinerant consultation clinic and was referred to the Washington University Rheumatic Fever Clinic where, because of marked tachycardia and obvious severe heart disease, he was sent into the hospital.

Physical examination at the time of entry revealed a temperature of 37.4°C., pulse 120, respirations 22 and blood pressure 150/30 mm. The patient was thin and undernourished but he was neither dyspneic nor cyanotic. One questionable petechial hemorrhage was observed on the cuticle of the third left finger. Examination of the eyes revealed no abnormalities. The upper respiratory tract appeared normal. The neck veins were not distended. The lungs were clear to percussion and auscultation. On inspection the entire left chest pulsated vigorously with each cardiac contraction. A thrill was palpated in the second left interspace, and one observer felt another thrill at the apex. The heart was enlarged 13 cm. to the left of the mid-sternal line in the sixth interspace; the rhythm was regular. At the apex a grade IV harsh systolic murmur was heard which was transmitted into the axilla and through to the back. A low-pitched mid-diastolic rumble was also heard at the apex. At the base a grade III systolic murmur and a loud high-pitched blowing aortic diastolic murmur were audible. The aortic second sound was loud and ringing. A capillary pulse was noted and Duroziez's sign was present. Examination of the abdomen re-

vealed that the liver edge was palpable just beneath the right costal margin. The remainder of the examination was not remarkable. There was no clubbing and no nodules were observed.

The laboratory data were as follows: Blood count: red cells, 3,680,000; hemoglobin, 12.5 gm.; white cells, 7,100; differential count, within normal limits. Urinalysis: specific gravity, 1.012; albumin, negative; sugar, negative; sediment: many granular casts, rare white and red blood cells. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 28 mg. per cent; fasting blood sugar, 72 mg. per cent; total proteins, 7.6 gm. per cent; albumin, 5.1 gm. per cent; globulin, 2.5 gm. per cent. Venous pressure: 168 mm. saline. Circulation time (arm to tongue with decholin): 37 seconds. Sedimentation rate: 3 mm. per hour. Blood cultures: negative. Chest roentgenogram: there was moderate generalized cardiac enlargement which included the left auricle. Convexity of the heart in its lower portion with some obliteration of outline suggested pericardial effusion. Electrocardiogram: P-R interval 0.17; Q-T interval, 0.32; rate 130; S-T segments depressed in leads I, II, AV_L, V₄, V₅ and V₆.

Although it was known that the patient had received some digitalis before entering the hospital, additional amounts were given cautiously. After he had received 1 gm. of digitalis leaf the patient became nauseated. A throat culture taken on admission revealed beta-hemolytic streptococci, and the antifibrinolysin titer was found to be 2+. Penicillin therapy was instituted. Three days after entry the patient's temperature suddenly rose to 38.8°C. He complained of arthralgia, anorexia, fatigue and palpitation. Subsequently his course was febrile, with elevations ranging from 38 to 39°C. Repeated urinalyses revealed persistent albuminuria and a few red cells in the centrifuged sediment.

One week after entry the patient was begun on cortisone therapy; he received 300 mg. on the first day, 200 mg. the second day and 100 mg. daily thereafter. On the fourth day of cortisone treatment the eosinophil count was 66 per cu. mm. and on the sixth day 187 per cu. mm. A second antifibrinolysin test was negative, and the white blood cell count ranged between 13,000 and 15,000. Subcutaneous nodules appeared on the right arm.

Because the patient had failed to improve on the dose of 100 mg. of cortisone daily, he was

given 200 mg. of the agent daily. The electrolytes were followed carefully and remained normal, but the non-protein nitrogen rose to 33 mg. per cent, and the white blood cell count to between 18,000 and 20,000 with normal differential counts. Repeated electrocardiograms showed only digitalis effect. The circulation time was 31 seconds, the venous pressure 150 mm. saline.

After seventeen days of continuous cortisone therapy the patient became edematous, rales appeared at both bases and the questionable ascites was noted. At that time the venous pressure was 270 mm. of saline, the circulation time 26 seconds, the non-protein nitrogen 39 mg., chlorides 96 mEq./L., sodium 132.4 mEq./L. and potassium 5.4 mEq./L. Cortisone therapy was discontinued. The patient was weak and extremely listless. He was given mercurhydrin with a good diuretic response, but subsequently his condition gradually deteriorated. He remained weak and apprehensive and had occasional cough and abdominal discomfort with nausea and vomiting. Rales persisted and ascites became evident, although by paracentesis only 70 cc. of yellow fluid were obtained. The non-protein nitrogen rose to 55 mg. per cent, the chlorides fell to 88 mEq./L., the sodium to 133.0 mEq./L. and the potassium rose to 8.6 mEq./L. The blood eosinophil count was zero; urinary output decreased.

Because of the findings suggesting adrenal insufficiency, the patient was given 2 cc. of lipo-adrenal cortical extract daily as well as glucose and saline infusions. He failed to respond, however, and continued to be dyspneic, weak and apprehensive. ACTH was then begun with an initial dose of 40 mg. followed by 80 mg. every six hours. On the third day of ACTH therapy the blood non-protein nitrogen was 122 mg. per cent, sodium 117.4 mEq./L., potassium 8.0 mEq./L., chlorides 82 mEq./L. and the blood pH 7.26. During this period dyspnea and orthopnea increased, the neck veins were full and the abdomen remained distended although the paracentesis wound continued to drain well. Moderate sacral and ankle edema were noted. Moist rales increased in both lungs. The urinary output remained small. On February 14, 1951, the patient suddenly developed syncope, his respirations became labored, the rales increased; and although he made a transient response to emergency measures, he expired rather suddenly.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Unlike some of the cases we have discussed in these conferences the primary diagnosis here is quite clear. This patient had acute rheumatic fever; his illness presented important problems which we shall attempt to cover in our discussion. It seems quite likely that the patient's first episode began with a sore throat and during the final episode, while he was in this hospital, beta-hemolytic streptococci were recovered from his throat. Dr. Harford, would you open the discussion by commenting on the current opinion in regard to the role of beta-hemolytic streptococcal infection in the pathogenesis of rheumatic fever.

DR. CARL G. HARFORD: I believe that it is well established that there is a definite connection between beta-hemolytic streptococcal infection and rheumatic fever, but the mechanism responsible for the development of rheumatic fever has not yet been elucidated.

DR. ALEXANDER: Would you summarize the current concept?

DR. HARFORD: I believe most persons interested in rheumatic fever believe that it is due to hypersensitiveness on the part of the host to the streptococcus or its products.

DR. ALEXANDER: Do you agree with that hypothesis, Dr. Glaser?

DR. ROBERT J. GLASER: Yes, I certainly do. As Dr. Harford has indicated, the mechanism is not as yet explained, but I believe there is little doubt that (1) patients who develop rheumatic fever have antecedent group A beta-hemolytic streptococcal infection and (2) the lesions of acute rheumatic fever are not *per se* infectious lesions; they are sterile. They represent instead an inflammatory response to an as yet undefined stimulus which involves group A streptococci. The lag period which usually ensues between the initial streptococcal infection and the development of rheumatic fever is thought by many to represent the period of sensitization.

DR. ALEXANDER: Since rheumatic fever is apparently related to streptococcal infections, what means may one use to prevent the infection and thus the disease?

DR. HARFORD: Probably the most practical and hopeful approach to the prevention of rheumatic fever is the use of chemoprophylactic agents which prevent streptococcal infection. Of the various drugs available I believe penicillin is the one of choice.

DR. ALEXANDER: How is penicillin administered for this purpose?

DR. HARFORD: Although the absorption of penicillin after oral administration is less satisfactory than when the drug is given parenterally, satisfactory levels can usually be obtained if 100,000 units are given twice daily. The group A streptococci are extremely sensitive to penicillin, and the evidence to date suggests that infection can be prevented in this manner.

DR. ALEXANDER: In connection with the relationship of streptococcal infection to rheumatic fever, Dr. Harford, would you comment on the use of the antifibrinolysin test? What is its significance?

DR. HARFORD: Positive antifibrinolysin tests are found in about 60 per cent of patients who have had hemolytic streptococcal infections. It is a test for a specific antibody response to infection with the streptococcus, and it is not therefore a test for rheumatic fever *per se*. A positive test only is of value in that it indicates that the patient has probably had a recent streptococcal infection. Unfortunately false positives may occur. We are now in the process of setting up the antistreptolysin "O" determination in the routine clinical laboratory. This test is quantitative, and is positive in a higher percentage of patients with recent streptococcal infections than the antifibrinolysin test.

DR. ALEXANDER: This patient developed rheumatic nodules. Would you discuss their incidence and significance, Dr. Glaser?

DR. GLASER: Nodules occur in 5 to 20 per cent of patients with acute rheumatic fever. Characteristically they are subcutaneous and may vary in size from 2 mm. to about 2 cm. in diameter. Often they are symmetrical and usually occur around bony prominences. Whether or not the appearance of nodules has diagnostic significance, I am not prepared to say definitively. In my experience the occurrence of nodules has often been associated with rather severe forms of rheumatic fever; it is thought by some authorities that nodules are a frequent concomitant of carditis and are thus to be identified with a poor prognosis. It is of interest in passing to note that the nodules of acute rheumatic fever and those of rheumatoid arthritis may be very similar both clinically and pathologically. The nodules of rheumatic fever ultimately disappear, whereas in occasional patients with rheumatoid arthritis we have seen nodules persist for years, and in one patient have seen actual suppuration of sub-

cutaneous nodules. Some pathologists believe that the nodules of rheumatic fever and of rheumatoid arthritis are indistinguishable histologically, but others, particularly Dr. Granville Bennett who has an extremely wide experience with the pathology of rheumatic diseases, believe that they can be distinguished.

DR. ALEXANDER: This patient, in the episode prior to the terminal one, had fever for ten months. Dr. Smith, would you comment on the pathologic changes probably taking place during that period?

DR. JOHN R. SMITH: It seems very likely that during that prolonged bout in which he was febrile, the patient's heart was involved with the rheumatic process, probably in the form of pancarditis. Ultimately, deformation of the valves appeared and his heart enlarged. This patient certainly developed progressive valvular disease as evidenced by the presence of both mitral and aortic involvement of rather severe degree.

DR. ALEXANDER: What lesions do you think will be found in the patient's heart?

DR. SMITH: I believe the heart will be hypertrophied, and that there will be both aortic insufficiency and mitral stenosis. It is also conceivable that the patient may have early aortic stenosis.

DR. ALEXANDER: It is noted that the patient had eight negative blood cultures. Do you believe that he had subacute bacterial endocarditis? He did have one splinter hemorrhage apparently and he had red cells in his urine. Further, his course was rapidly downhill.

DR. SMITH: I doubt seriously that he had bacterial endocarditis.

DR. ALEXANDER: Do you believe the patient had bacterial endocarditis, Dr. Scott?

DR. VIRGIL SCOTT: I think that would be extremely unlikely. I believe he will have vegetations, but they will not be bacterial but rather rheumatic in type.

DR. ALEXANDER: This patient was treated with cortisone for seventeen days. Dr. Glaser, would you comment on the collective experience in various clinics concerning the use of ACTH and cortisone in acute rheumatic fever?

DR. GLASER: It is, of course, much too early to evaluate definitively the value of ACTH or cortisone in the treatment of patients with rheumatic fever; there have been both favorable and unfavorable reports in the literature. When patients with rheumatic fever are given either

ACTH or cortisone, they usually exhibit a fairly dramatic response in so far as temperature, arthritis and general constitutional symptoms are concerned. Whether or not the pathologic changes which accompany acute carditis are controlled is not certain, although in some of the reported cases the signs of carditis have disappeared promptly after the institution of therapy. Our experience in this hospital to date has not been particularly favorable. We have had one girl about seventeen who has made what I consider to be a satisfactory response, but we have had several others whose symptoms and signs have not been affected by the drug. In our experience as well as in the experience of other investigators neither agent has proved beneficial in a number of patients with the "smoldering" form of rheumatic fever. In young adults whom we see in this hospital that particular group is especially important since the patients in their late teens and early twenties who get monocyclic rheumatic fever usually recover promptly and often escape permanent heart disease. In the Children's Hospital Dr. Goldring's results have been similar to ours; he, too, has not been favorably impressed with the effectiveness of ACTH or cortisone in the chronic or smoldering forms of the disease.

Probably one of the most important points to make is that the evaluation of cortisone and ACTH in rheumatic fever will require at least three to five years. A large series of cases must be collected and followed closely for that period of time in order to determine the incidence of permanent heart disease in patients so treated. Such a study is now under way in a number of cooperative clinics. At present it is our belief that ACTH or cortisone should be used in the treatment of rheumatic fever with the hope that at least in some instances they will prevent serious cardiac damage.

DR. ALEXANDER: You indicated that the constitutional symptoms are often controlled promptly with either of these agents.

DR. GLASER: There is no question that fever, leukocytosis and arthritis usually respond quite satisfactorily. The sedimentation rate comes down at a slower rate. It is well to remember, of course, that aspirin often achieves the same results. Unfortunately control of the arthritis per se is not the most important therapeutic aim in rheumatic fever. It has been said that rheumatic fever is the disease which "licks the joints and bites the heart," a statement which

emphasizes the fact that arthritis, no matter how severe in the acute state, has little import from the long range point of view in that apparently all patients with rheumatic fever recover completely from the arthritic manifestations. On the other hand the occurrence of acute carditis, as has been indicated, often leads to permanent heart damage.

DR. ALEXANDER: This patient, prior to coming to the hospital, had received salicylates over a long period of time. Would you comment on their use in rheumatic fever?

DR. GLASER: As we have stated ACTH or cortisone is the drug of choice at present. Because of their cost, however, it may not be possible to give them to all patients, and under those circumstances salicylates or perhaps 2-hydroxy-phenyl cinchoninic acid should be used.

DR. ALEXANDER: How effective are the salicylates in rheumatic fever? They have been used in the disease for many years.

DR. GLASER: In most instances they bring symptomatic relief. I believe there is no clear cut evidence, however, that they protect against permanent cardiac damage. Some years ago it was postulated that intravenous salicylates in large doses would prevent carditis, but I believe that that concept has been discarded in most quarters. In an experimental study Dr. George Murphy, then at Hopkins and now at the Rockefeller Institute, found no histologic evidence that salicylates inhibited the rheumatic process.¹

DR. HENRY A. SCHROEDER: Dr. Alexander, I believe the question as to whether cortisone or ACTH is preferable in the treatment of rheumatic fever is an important one. Cortisone is a single adrenal hormone and depresses the adrenal when used over a long period of time. ACTH, on the other hand, stimulates the whole adrenal gland and perhaps would be more desirable.

DR. ALEXANDER: Would you comment on that point, Dr. Daughaday?

DR. WILLIAM H. DAUGHADAY: I do not believe that we know enough as yet about the relative merits of ACTH and cortisone. Cortisone has the advantage over ACTH in the treatment of patients with rheumatic fever in that it is less apt to cause severe edema or hypertension.

DR. ALEXANDER: Dr. Daughaday, at the end of seventeen days of therapy with cortisone the patient was noted to have edema, hyponatremia,

and hyperkalemia. Would you discuss these developments.

DR. DAUGHADAY: The question to be answered in this particular case was whether the patient had adrenal insufficiency secondary to prolonged cortisone therapy, or whether there was a functional disturbance of the kidney secondary to severe, chronic congestive failure. In the latter situation renal plasma filtration may be markedly decreased. Apparently the staff following the patient on the ward thought that there was a significant degree of adrenal insufficiency, and for that reason administered adrenal cortical extract. It would be quite unusual to find marked edema in the presence of adrenal insufficiency; usually such patients lose water about as fast as they lose sodium, and they become markedly dehydrated. It is quite clear that this patient, on the other hand, was losing sodium and chloride at a faster rate than he was losing water. As a result he developed the very damaging low salt syndrome plus edema and, as Dr. Schroeder has clearly demonstrated, renal function suffers further deterioration under those circumstances.² I cannot say with any conviction that this patient died of adrenal insufficiency although it certainly has to be considered in view of the large doses of cortisone he received. In general, it is probably better to discontinue cortisone gradually than to stop it abruptly; in that way adrenal function can gradually return to normal so that when the cortisone is finally stopped, the patient does not exhibit signs of adrenal insufficiency.

DR. ALEXANDER: This patient exhibited marked prostration. Is that attributable to the withdrawal of hormone therapy?

DR. DAUGHADAY: In order to answer that question I think it would be better to consider a simple case, namely, a patient with rheumatoid arthritis, without heart disease, treated with cortisone for a long period of time. If one should suddenly stop cortisone, the patient would complain of lethargy and weakness; and if he had accumulated any edema during the course of cortisone therapy, he would lose it rapidly and possibly become slightly dehydrated. These signs have been attributed to transient adrenal insufficiency; during this period the atrophic adrenal cortex regains function. There are reports of patients who have had severe difficulty during this period. In my experience

¹MURPHY, G. E. Salicylates and rheumatic activity. *Bull. Johns Hopkins Hosp.*, 77: 1, 1945.

²SCHROEDER, H. A. Renal failure associated with low extracellular sodium chloride. *J. A. M. A.*, 141: 117, 1949.

such patients have had mild or moderate symptoms but no really serious ones.

DR. ALEXANDER: Should ACTH be given as cortisone is discontinued?

DR. DAUGHADAY: One can certainly give ACTH before discontinuing cortisone in order to stimulate the adrenal or, as already indicated, cortisone can be discontinued by very gradual steps so that the patient regains normal adrenal function before cortisone is stopped entirely.

DR. ALEXANDER: Dr. Schroeder, this patient had hypochloremia despite the fact that he was being given salt. Would you comment on this finding.

DR. SCHROEDER: This is a complex situation in which renal, adrenal and cardiac components contributed to overhydration and the development of the low salt syndrome. Renal function is reduced in congestive circulatory failure, especially the ability to excrete salt and water. In some cases excess water is retained. The cortisone and more especially the ACTH increased markedly this renal disturbance. It is difficult to explain the high potassium, for it is often low in the low salt syndrome, unless we remember that plasma potassium levels merely reflect a balance between intake, cellular exchange and excretion and are not indicative of cellular potassium concentrations. In this situation potassium has probably been lost from cells, while sodium and water has entered them. The high plasma level therefore may indicate cellular loss and failure of renal excretion. The ability of the kidney to handle potassium is one of the last functions lost in renal disease. Therefore, it would not surprise me at all if this patient had acute nephritis in addition to the low salt syndrome induced by ACTH. He had fever, albuminuria which developed under observation and a rising non-protein nitrogen. It is obvious that the hyponatremia was not reversed because he did not receive enough molar sodium chloride and did not have his fluid intake restricted enough to raise his electrolytes to normal. That objective can always be accomplished if one gives enough salt.

DR. ALEXANDER: Dr. Glaser, what about the concomitant incidence of acute nephritis and rheumatic fever?

DR. GLASER: The general consensus has been that glomerulonephritis and rheumatic fever occur together in approximately 1 per cent of patients. Several months ago, however, in the American Journal of Medicine, Hartman and

Bland reported that 5 per cent of a large group of patients with rheumatic fever also had glomerulonephritis.³

DR. SAMUEL C. BUKANTZ: It is of interest in regard to the possible occurrence of a renal lesion that in Dr. Rich's recent experiments in which he gave cortisone to rabbits to prevent serum disease, he found that while both cortisone and ACTH suppressed the usual glomerular lesions which characterize hypersensitiveness to foreign protein in rabbits, the rabbits treated with cortisone developed glomerular lesions which were apparently due to the steroid per se.⁴ The significance of this lesion in terms of human patients treated with cortisone is not as yet known.

STUDENT: Would Dr. Schroeder comment on the continued use of ACTH in a patient with congestive failure?

DR. SCHROEDER: It is contraindicated because it causes further retention of salt and water.

DR. ALEXANDER: In summary, we would agree that this boy had acute rheumatic fever with carditis, superimposed on chronic rheumatic heart disease. In addition, he had heart failure and possibly acute nephritis.

Clinical Diagnoses: Acute rheumatic carditis; rheumatic heart disease with mitral stenosis, aortic insufficiency and ? aortic stenosis; cardiac insufficiency; ? acute glomerulonephritis.

PATHOLOGIC DISCUSSION

DR. JAMES C. ROBERTS: The heart was greatly enlarged and extended over approximately two-thirds the width of the thorax. Because of limitations imposed by the autopsy permission, exact weights of the viscera could not be determined but the heart was estimated to weigh over 500 gm. The pericardial cavity was obliterated by fibrous and fibrinous adhesions. On the tricuspid, mitral and aortic valves there were small smooth verrucae a millimeter or less in diameter that lay approximately along the lines of closure. At the center of the base of each aortic cusp there was an irregular calcified nodule 1 cm. long, covered by endothelium that extended into the left ventricular wall. The left

³ HARTMAN, S. A. and BLAND, E. F. Rheumatic fever and glomerulonephritis, a clinical and post-mortem study. *Am. J. Med.*, 10: 47, 1951.

⁴ RICH, A. R., BERTHRONG, M. and BENNETT, I. L. The effect of cortisone upon the experimental cardiovascular and renal lesions produced by anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 87: 549, 1950.

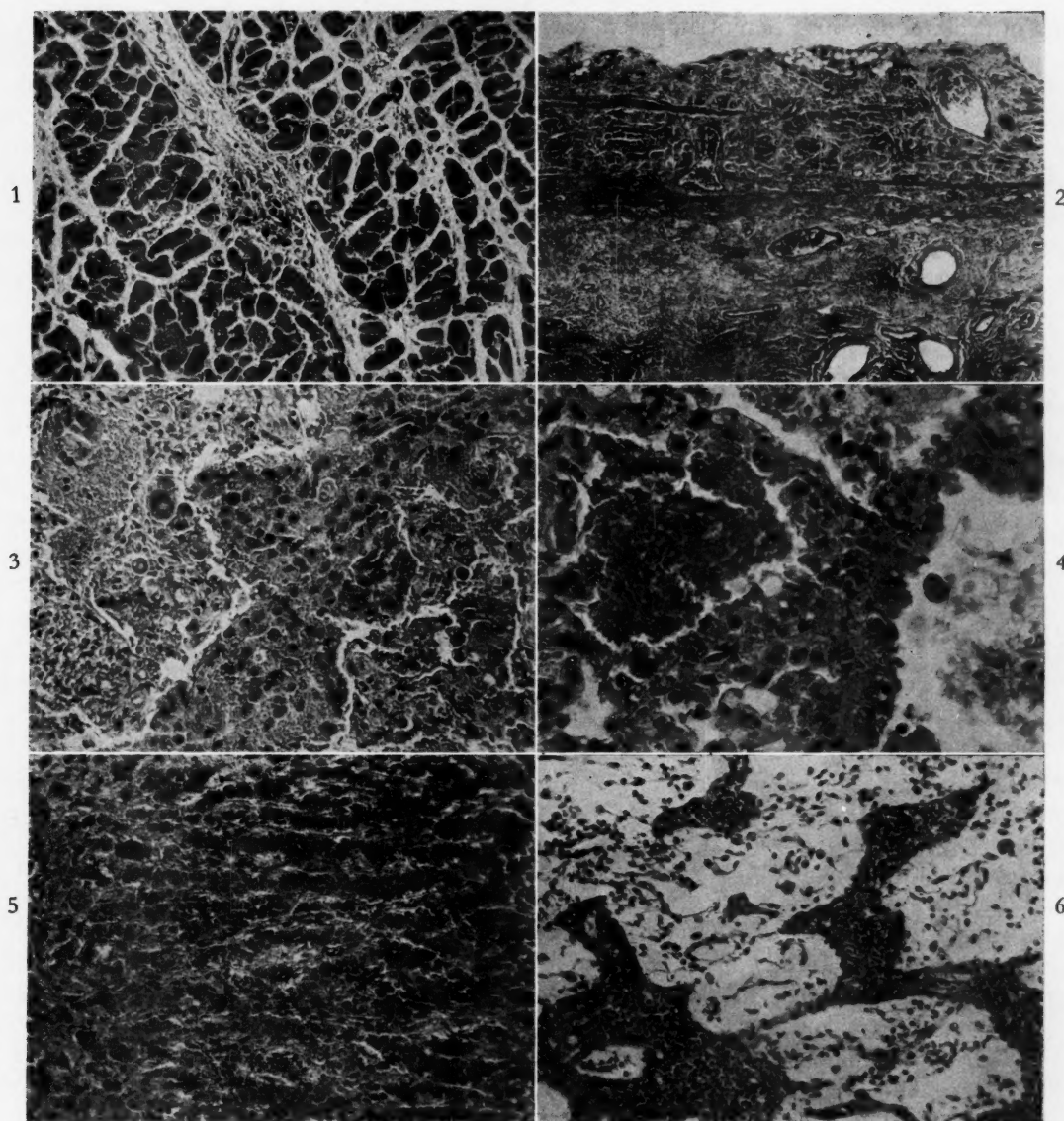


FIG. 1. Myocardium with an Aschoff nodule, edema and slight increase of interstitial fibrous tissue.

FIG. 2. Fibrous obliteration of the pericardial space; the dense collagenous fibers in the upper portion are typical of parietal pericardium and a few myocardial fibers are present at the lower edge.

FIG. 3. Mononuclear exudate and hemorrhage in the pulmonary alveoli with thickening of alveolar walls due to infiltration by mononuclear cells.

FIG. 4. Rheumatic pneumonia with a fibrinoid membrane over a zone of bland necrosis in the wall of the alveolus on the right.

FIG. 5. Adrenal cortex showing lipid depletion. Although the patient received ACTH and cortisone, this appearance of adrenals can result from the effects of debilitating disease alone.

FIG. 6. Extreme dilatation of sinusoids and lymphoid depletion in a mesenteric lymph node.

atrial endocardium was thickened throughout with fibrous tissue. The myocardium was flabby but otherwise not grossly remarkable. Edema and congestion greatly increased the weight of the lungs. Fibrous and fibrinous adhesions were present over the left lung and the lower lobe of the right lung. Particularly inferiorly and posteriorly, there were large irregular areas of firm and rubbery, dark red parenchyma. The

blood vessels leading to these areas contained no thrombi or emboli. The liver was of a typical "nutmeg" appearance with dark red lobular markings surrounding small yellow zones. The spleen was slightly enlarged and the white follicles were obscured. The adrenals were remarkable only in that the cortex was not yellow. The kidneys were congested but otherwise normal. The lymph nodes were small, pale and

soft; loss of architecture and hemorrhages were prominent in all these nodes examined.

DR. EDWARD B. SMITH: The principal gross pathologic alterations were in the heart and lungs; the kidneys were grossly normal. By microscopic examination the verrucae on the various valves were well organized structures without fibrin or bacteria on their surfaces. Figure 1 is of a section of the myocardium that presented rather classical Aschoff nodules with the typical cells and a certain amount of edema of fibrous septa. The myocardial fibers in this field were otherwise normal, except perhaps for a slight increase in fibrous tissue. In other sections there was more extensive focal interstitial fibrosis that was evidence of the duration of this disease or a residue of previous attacks. In Figure 2 the upper portion shows the characteristic thick collagenous bundles of the parietal pericardium. Beneath that was a zone of scar tissue that obliterated the pericardial sac. There was a moderate amount of cellular activity in this zone, and beneath it particularly we found many Aschoff nodules.

In sections of the lungs (Fig. 3) there was a heavy exudate of mononuclear cells in some alveoli and extravasated erythrocytes in many others. The alveolar walls were thickened by an increased number of mononuclear cells. Figure 4 illustrates the bland necrosis which occurred in alveolar walls. Along the wall of the alveolus on the right side of the photograph there is a layer of fibrinoid material over a zone of cells that have lost their nuclei. This lesion is characteristic of rheumatic pneumonia or rheumatic pneumonitis. The other alveoli show the mononuclear infiltration of their walls and one is filled with hemorrhage. In the liver there was extreme congestion with central necrosis and slightly increased amounts of fibrous tissue about the central veins and along the sinusoidal basement membrane. This represented both chronic and acute passive congestion.

The adrenal cortex, as shown in Figure 5, was devoid of fat vacuoles. Lipid depletion is characteristic of any prolonged severe disease in which there is wasting of the patient; and there were no changes we can recognize as

specifically due to the ACTH or cortisone which this patient received. A few lymphocytes were scattered throughout the section but those, too, are found after nearly all prolonged illnesses. Figure 6 illustrates a very interesting section of a mesenteric lymph node. There were widely dilated sinuses filled with lymph or edema fluid and advanced lymphoid depletion. This picture probably resulted from a summation of the effects of the debilitating disease, the edema of cardiac failure and possibly the lysis of lymphocytes by the therapeutic agents employed.

The kidney contained no significant histologic changes. I do not know that we can explain the clinical evidences of renal damage very well, but hematuria and albuminuria do occur in many infectious diseases as well as in congestive failure. The non-protein nitrogen was particularly high to have been due only to cardiac failure, but there was no other apparent explanation. Otherwise this was a fairly classical case of rheumatic fever in which there was the additional feature of rheumatic pneumonitis.

DR. WILLIAM D. PERRY: Are calcified lesions at the bases of aortic cusps a usual finding in rheumatic heart disease?

DR. SMITH: We interpret the lesions at the base of the aortic cusps in this case as a result of an earlier attack of rheumatic fever. Their position and configuration were unusual but did not suggest any other etiology.

DR. SCHROEDER: In retrospect this patient must not have received adequate salt replacement therapy. In the presence of oliguria it should not be impossible to elevate the salt concentration in the body if adequate amounts of sufficiently concentrated fluids are given. I think the patient probably died of the low-salt syndrome.

Final Anatomic Diagnoses: Chronic endocarditis of the left atrium and of the aortic valve; acute rheumatic pancarditis, recurrent; acute rheumatic pneumonia; chronic and acute passive congestion of the liver and spleen.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Clinic on Psychosomatic Problems

A Case of Asthma Treated with Psychotherapy

THESE cases are chosen to illustrate the relation between psychiatric and medical factors in the production of symptoms. They are part of the Harvard teaching on the Psychiatric and Children's Medical Services of the Massachusetts General Hospital. These psychiatric conferences are edited by Drs. Stanley Cobb, Harley C. Shands, and Henry H. W. Miles. Publication is made possible by a grant from the Josiah Macy, Jr., Foundation.

DR. HARLEY C. SHANDS: The case for discussion is that of Mrs. C. J., a thirty-nine year old woman, who entered our ward with complaints of asthma and chronic fatigue. I will first summarize the principal facts in her family background and medical history and then go on with the interview material which has emerged in the course of her two months' stay here.

The patient was the youngest of four children; the first two died in infancy. The surviving sibling was a brother two years older, and the patient had always believed he was preferred and pampered by her mother. Her father had died when she was three months old. The mother had very rigid standards of conduct and the patient had never been able to discuss any intimate problems with her. Following the father's death there had been much economic difficulty and the mother had been forced to run a rooming house to support the family.

Significant illnesses included scarlet fever at the age of seven and rheumatic fever with cardiac involvement at twenty-two. The patient had suffered from dysmenorrhea since the menarche at the age of thirteen. Hay fever developed when she was eighteen years of age and she continued to have it each year in the July-October period. When the patient was thirty asthma suddenly developed, which became progressively worse. When she was thirty-six she was unable to get out of bed during the last half of her pregnancy because she was having so much trouble with asthma. She

has been under treatment for several years in the Allergy Clinic.

Other complaints at the time of admission included severe neck pain which was relieved with massage, stuffiness of her nose during cold weather, chronic cough with a dull ache and "heavy feeling" in her chest and the production of yellowish sputum with upper respiratory infection. Chronic fatigue, unrelated to exertion, has been a prominent symptom.

Psychiatric observations are as follows: The patient's earliest "memory" was a story that had been told her of her father. On his deathbed he got up, went over to her cradle, fondled her and said, "Daddy's darling." He then went back to bed and died. The patient always had thought life would have been much smoother with a father, and she described doctors she liked as being very "fatherly." As the patient grew up, she had to do a lot of work to help her mother and always believed her mother had no time for her. In addition the mother's rigid standards of behavior precluded the enjoyment of many things which the patient thought would be pleasant. She was not allowed to dance or play cards and on Sunday the prescribed entertainment was hymn singing.

She remembered several sexual episodes from her childhood. When seven years old she was very much embarrassed when a doctor exposed her abruptly in order to look at a rash. In the next year or two she was fondled and undressed on several occasions by an elderly male acquaintance. In

our interviews this has been an extremely difficult topic for her to discuss.

At eleven she was pleased when her mother became engaged to a man who seemed to like the patient very much, but then was greatly disappointed when her brother broke up the match by threatening to run away if the mother married again. At twelve she quit school because she did not like the teacher. Her menarche occurred at thirteen; she was frightened and thought she had been injured. Her mother's only comment was that this would happen every month and she must stay away from boys. Later in the same year she was sent away to work as a housekeeper and while there was raped by her employer's lover. She immediately returned to her mother but could not tell her of the episode; her mother was annoyed that she had lost the job. At fourteen she was the object of another attempted assault; again she could not cry out. From this time on she had a mild hand-washing compulsion.

At the age of sixteen she was married to a twenty-four year old friend of her brother's. This marriage lasted for about three years but she lived with her husband less than one year. She believes they had intercourse only five or six times and it was very painful. She was extremely ashamed at the idea of having intercourse in her mother's house and soon found that her husband was alcoholic, enuretic and provided no money for her. They separated and he obtained a divorce.

After the separation, when she was about eighteen, she began to go out with young men and remembers that she would encourage them to be affectionate, to hug and kiss her, but as soon as they began any specifically sexual advances she would become terrified and go home as quickly as possible. During this period she was particularly conscious of her brother's rejection of her. She continually felt hurt because he never seemed to show any interest in helping the patient have a good time or taking her with him when he went out.

At the age of twenty she met an honest,

industrious, upright man who met with her mother's approval. They became engaged but she avoided marriage. He was extremely jealous and resented her paying any attention to anyone else. Finally after five years she decided to break the engagement and did so by wrapping his ring in toilet paper and dropping it into the open stove in the living room in his presence. During this episode her throat felt painfully constricted and she was unable to eat for the remainder of the day.

For the next five years she worked in a shop and would come home every evening exhausted and very tense. At this time she said that her only way of obtaining relief was to have a crying spell. She would then feel relieved enough to be able to swallow her dinner.

When the patient was thirty she met her second husband, a man six years her junior. At first she had very little interest in him because of the difference in their ages but eight months later, after he had repeatedly asked her to marry him, she agreed. After they were married she believed she had never been so happy in spite of the fact that intercourse was never pleasant.

The first attack of asthma occurred soon after her marriage. Her husband had gone to a sporting event with one of his friends. They refused to take the patient because they said she would get too excited. She was very much upset over this rejection and cried a great deal while alone that night. She was unable to sleep and continued to cry until her husband finally came in drunk at 4 A.M. She was then even further upset when he arose at his customary hour and went off to work as though nothing had happened. It was very difficult for her to get up that morning and she became more and more tired as the day progressed. She thought that if she walked downstairs she probably would not have strength enough to walk back up. She cried some more and her chest began to feel "tight and wheezy." She could not eat any lunch. By the time her husband came home that night she was wheezing so severely that he called a doctor

who gave an injection of adrenalin. From this time on asthmatic attacks occurred whenever her husband went out without her.

Somewhat later in the marriage there was a period of eighteen months during which her husband was very attentive and stayed home all of the time with her. For this whole period she was almost completely free of asthma. In response to her husband's urging she underwent several minor gynecologic operations in an effort to become pregnant, and finally succeeded. The extent of the difficulty in communication between this patient and her mother was demonstrated by the manner in which the pregnancy was discussed. For several weeks the patient was unable to tell her mother about it but finally managed to blurt it out one morning as she was helping prepare some ingredients for pickling. The mother received the news in silence and then commented, "I have to go look at the pickles." The matter was never again discussed between them.

In spite of the husband's wish that the patient become pregnant he displayed little interest in the event and again became inattentive. The patient began to have more asthma and finally spent the last half of the pregnancy in bed. During this time visits from the husband's sister were regularly followed with severe asthmatic attacks.

The week after the birth of her baby, a boy, she was upset because her husband visited so infrequently at the hospital. The day she went home he said abruptly that he was leaving and promptly moved his possessions out of the house. She went to her brother's house where she stayed for the next few months. During this time she was depressed and cried most of the time, but she was free of asthma.

When she felt better she took a job as housekeeper for a divorced man and soon found herself once more involved in a sexual relationship. She felt very guilty, and depressed about this; her husband would phone her occasionally at midnight when he had been drinking, and after each call she had an asthmatic attack.

From this point on her health became worse and she spent most of her time in bed or in hospitals. Her child was a constant problem and she frequently had to leave him with her husband's family for long periods while she was sick. Her mother worked as a housekeeper for an elderly bachelor and was unable to be of any assistance to her.

The patient was referred to the Psychiatric Clinic because of the intractable nature of her asthma in the hope that some emotional problems might be discovered and alleviated. The patient expressed a great deal of fear at the idea of being seen by a psychiatrist, but kept the appointment and eventually agreed to enter the hospital for a period of therapy in the psychiatric ward.

Her hospital course has been remarkable. After two or three days of discomfort at being "a psychiatric patient" she lost all of her symptoms. She has been energetic and friendly and has participated in all of the ward activities with enthusiasm. She has mentioned many times how luxurious she finds the ward and says that she has never enjoyed herself so much. She is very popular with the other patients and has become a sort of mother figure to them; they bring her their troubles and complaints about the doctors. She became involved briefly in a mild flirtation with a middle-aged male patient.

After two weeks in the hospital she began to discuss with very great reluctance some of the sexual material I have already outlined. As the interviews progressed, she began to complain of a recurrence of her old symptoms; the first to reappear was the chronic fatigue and listlessness. Following some of the more painful therapeutic sessions she noticed mild wheezing. During this period she talked a good deal about the preoccupation she has always had over being conspicuous; she has never, for instance, been able to eat in a brightly lighted restaurant or to dance in a public place unless it is so dimly lighted as to make it impossible to recognize other people.

DISCUSSION

MISS EVELYN STILES: We have known Mrs. J. in the Out-patient Department. The social worker tried to help her make arrangements for her little boy so she would be free to enter the hospital. She has been irregular about keeping appointments. We were able to arrange a place for him to be cared for, but then the patient left him with her in-laws. Even so, she has worried about the boy, fearing the mother-in-law would become ill and that she would have to leave the hospital before she was well enough. She has been afraid her in-laws would take the boy's love away from her. In the ward she wanted to see the boy but hated to ask her in-laws to bring him.

DR. JACOB E. FINESINGER: Is the patient capable and able to manage things in the world?

MISS STILES: I have the impression she might be quite capable if she were not so much hampered by her tendency to feel guilty in all of her relationships.

MRS. EUNICE ALLEN: I saw her about a year ago. She showed the same charm of manner and capacity to talk about good plans, but nothing ever materialized. We were trying to make some living arrangements for her which excluded her relatives. It seems characteristic that something happens in the reality situation over and over again.

DR. FINESINGER: Does she have difficulty in making up her mind?

DR. ERICH LINDEMANN: It is not so much that she is unable to decide between two possibilities; she gets herself into social situations in which she is helplessly caught in a dilemma, in which the decision is no longer hers. It appears on the surface like an inability to decide between two courses of action, but the important thing is the situation rather than a compulsive inability to make up her mind. Her conflicts tend to express themselves in "acting out" or in the asthmatic attacks rather than in neurotic symptom formation.

DR. FINESINGER: She is an attractive

woman without too many psychoneurotic symptoms except when under a lot of tension. She has a certain amount of sensitivity to allergens. There are some definite correlations between the asthma and specific situations. She has talked along and you have some material but there are things you have not been able to get at.

DR. SHANDS: She says it is distressing to her that people other than me are acquainted with the interview material. When the doctors make ward rounds, she can only look at the one who speaks to her. She thinks the doctors must disapprove of her because of the "bad things" she has told me.

DR. FINESINGER: The major problem which comes up at once is rejection. The Chicago group¹ found that to be the characteristic problem in asthma. Exhibitionistic trends were not seen so often. The mild compulsive hand washing which this patient described is not infrequent in atopic dermatitis and also in asthmatics according to the Chicago group.

DR. BARRY BIGELOW: I noticed the lack of conscious feelings of anger or indignation. The patient has never allowed herself to express any of the aggressive aspects of her personality. Instead of that, she has a lot of guilt reactions as though she were worried about having hostile feelings. Perhaps that gives us a lead as to what she needs. If she can develop a relationship with Dr. Shands which will permit her to express some of these feelings, or at least formulate them, it would be helpful.

DR. SHANDS: The only expression of aggression she has mentioned is that at times she becomes angry with herself and scolds her image in the mirror.

DR. EDWARD HITSCHMANN: We see a cheerful patient who is improved. She does not appear to believe in allergy or in psychotherapy. The material dealing with an intense erotic life, early sexual experiences,

¹ FRENCH, T. M., ALEXANDER, F. et al. Psychogenic Factors in Bronchial Asthma. *Psychosom. Med.*, Monographic Series, vol. 2, no. 1 and 2. National Research Council, Washington, 1941.

rape fantasies, and so on, with reluctance and shame, almost justifies a diagnosis of hysteria. The weakness of our theoretic understanding of psychosomatic problems is demonstrated here because with the passiveness, fear of disapproval, fear of being conspicuous, etc., it would seem that she ought to have a skin disease or a blushing neurosis.

DR. FINESINGER: What can we do for her?

DR. LINDEMANN: I am not sure what the best sequence of therapeutic action would be. Dr. Hitschmann's point about the first impression being that of hysteria is well taken, but that is only the first impression. The relationship which this patient has developed with her therapist is not the kind we see in hysteria in which there is the development of a great deal of interest in the therapist. Instead we see what looks like a confession compulsion; she tells him over and over again how bad she really is and that he ought to disapprove of her. She tests him again and again and there is always the suggestion that worse things are yet to come. The relationship is quite rigid and has not changed much.

If one probed for specific material, would the relationship change? It may be that the most effective type of therapy here would be one in which the patient has an opportunity for repeated confession without censure. There is a good chance after discharge that she may get involved in dramatic difficulties where it will be very hard to approve of her. If we handle her in the clinic, there should be another person involved. This other person could check some of her behavior patterns more than her therapist could; for instance, a social worker might say, "It would be better not to do so-and-so now."

DR. FINESINGER: Could one begin by explaining the psychologic patterns to her? If this fails repeatedly, I should then agree there is no point in exploring and would try situational therapy.

DR. LINDEMANN: I agree with that. These asthmatic patients are apt to be very dependent and frustrated. The situation is

quite different from that in the psychoneuroses since the organ involved in the disease is not the focus for fantasy formation.

DR. FINESINGER: In a neurosis the organ concerned has some symbolic value, but with these patients the fantasy is secondary to the existence of a disease. After getting asthma they are concerned with the chest. With hysteria the concern is with fantasy. Psychoneurotic symptoms are more highly integrated than are psychosomatic symptoms.

COMMENT AND FOLLOW-UP

This case was selected to illustrate some of the problems and technics involved in the treatment of a patient with severe bronchial asthma. Her original contact with the hospital had been through the Allergy Clinic where several years of medical treatment had not helped her. Referral to the Psychiatric Clinic had come as a "last resort." This in no way implies a criticism of the allergists, as it would impose an impossible demand on the time of the psychiatric staff even to see in consultation large numbers of such patients, much less attempt therapy. Obviously, only a minute percentage of them can be accepted for long term psychotherapy.

We believe this case is especially interesting because the patient has maintained contact with us for five years and a report of her subsequent course will demonstrate some of the vicissitudes which may be expected in this sort of therapeutic relationship.

The patient has been seen in the Allergy and Psychiatric Clinics, the former quite regularly and the latter somewhat less so. Throughout this period the long term therapeutic burden has been carried by the psychiatric social worker in sessions about twice a month. From time to time the patient has developed additional symptoms when under unusual stress and has requested to see the psychiatrist again. Several times these periods of upset have been the occasion for further psychologic exploration.

For the first few months after leaving the hospital the patient worked most of the time upon the problem of her relationship with

her husband. She finally decided that the marriage had no prospect of further satisfaction to her and went through with a divorce.

In the year following discharge after two attempts to work out living arrangements with women of her own age, both of which ended in failure, she found that she could rent a small apartment in the house where her mother worked. She has remained there since, and in spite of a good deal of friction between her and her mother and some distress because the child's noisiness is somewhat disturbing to her mother's employer, it seems clear that she gets a good deal of support from the close relationship with her mother. They have been able to remain on much easier terms than had previously been possible.

On one occasion the patient returned for a period of rather intensive work with the therapist because of her difficulties with her son. She could not understand why she should be so angry with him so frequently. In the investigation of this problem she gained a good deal of insight into her feelings about the boy, especially in relation to her previous difficult relationships with her brother and two husbands. She has been able to modify her hostile and over-protective attitude toward him to some degree and to react to the anger with less guilt.

There have been two transient relationships with men which have not developed to the point where she has been greatly concerned with them. She still feels a good deal of discomfort at entertaining men at home because of her mother's presence in the house. She continues to feel quite conspicuous in any public gathering but she has been able to join in some community enterprises with pleasure.

The status of her asthma has fluctuated considerably. When she entered the ward, the physicians in the Allergy Clinic were greatly concerned about her because of the intractable state of the disease. The sharp relief of the asthma which occurred in the psychiatric ward and persisted for a number

of months after her discharge was very striking; it resembled the halcyon period with her husband in which she had no serious symptoms for eighteen months while he was attentive. The summer following discharge the patient had an attack which was severe enough to necessitate care in the emergency ward for a few days. Since that time, however, she has not been hospitalized. The asthma has persisted to some degree much of the time; the patient continues to need adrenalin by inhalation and by injection upon occasion.

Evaluation of the psychotherapy in this case cannot be made on a precise and objective basis. The opinion of the psychiatrists and social workers who have followed up the patients' progress is that she has made a great improvement in her interpersonal relationships; there is no question, however, that she is still hampered by her emotional difficulties. It is impossible to compare the present status of her asthma with the situation which might have existed had she not received psychotherapy at all since asthma is a notoriously unpredictable disease in any case. We are left then with only two lines of evidence, neither of which is of much scientific value: one is the opinion of the psychiatric team and the other is a rather touching gratitude and enthusiasm on the part of the patient. A case such as this one emphasizes in a striking manner the difficulties in assessing the results of psychotherapy and the necessity of further research to develop satisfactory methods of evaluation. Many of us believe that psychotherapy more closely resembles an *educational* process than one of *treatment* in the usual medical sense; in this context we believe it is a safe statement that this patient has learned a great deal about her potentialities and her limitations. On the other hand, she has experienced very little change in the fundamental tendencies present in her personality. The improvement which has occurred is a "decrease in the denominator" rather than an "increase in the numerator."

Case Reports

Treatment of Cardiospasm with Adrenergic Blockade*

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MEDICAL management of cardiospasm (achalasia of the cardia) has been notably ineffective. Nitrites give relief in some cases but their effects are transient and tolerance usually develops rapidly. The belladonna alkaloids have been employed as extensively as any agent but the results have been unimpressive. Physostigmine and neostigmine have also been used with equally unsatisfactory results. The employment of such diametrically opposed forms of therapy emphasizes our lack of knowledge of the basic pathologic physiology of this condition. Although the major part of the gastrointestinal musculature is stimulated to contract by the parasympathetic (cholinergic) nervous system, the sphincters are in general stimulated by the sympathetic (adrenergic) system. Consequently it appeared worth while to test the ability of an effective adrenergic blocking agent to relieve functional obstruction of the cardia although the existence of a true sphincter between the esophagus and the stomach has not been conclusively demonstrated.

CASE REPORT

W. E. P., a fifty-six year old unemployed miner and railroad worker, was admitted to the Salt Lake Veterans Hospital on January 13, 1949, complaining of abdominal distress of thirty years' duration. During most of this period the primary symptom was a dull, aching discomfort in the right upper quadrant which was relieved by food and alkali. In 1921 gastrointestinal x-ray studies were performed and the patient was told that he had a duodenal ulcer. His symptoms were controlled fairly well on a

medical regimen until one year prior to admission when episodes of epigastric discomfort became more frequent and persistent. Appendectomy was performed elsewhere six months prior to admission in the hope that this would relieve the distress but it failed to alter the condition. During the four months prior to admission the patient noted a distended, bloated feeling, burning pain in the epigastrium and the passive regurgitation of food ingested one to two days previously. Vomiting, which was voluntarily induced, provided considerable relief from the discomfort. A 30 pound weight loss occurred during the year prior to admission. No hematemesis, melena, acholic stools or jaundice was noted.

Physical examination revealed a tall, thin, white male who did not appear to be acutely ill. Blood pressure, temperature, pulse and respiration were normal. Epigastric tenderness was noted but no abdominal organs or masses were palpable. Laboratory studies disclosed a normal blood picture, a normal gastric secretory response to histamine and normal liver function. Gastrointestinal x-ray studies demonstrated dilatation of the lower two thirds of the esophagus, with marked retention of barium. (Fig. 1.) Fluoroscopy revealed apparent spasm of the cardioesophageal junction, with only a very fine stream of barium passing into the stomach at irregular intervals. About half of the administered barium was found in the esophagus five hours after administration (Fig. 2) and a considerable amount remained at eighteen hours. There was no evidence of an esophageal ulcer but the duodenal bulb was deformed. Esophagoscopy under

* From the Departments of Pharmacology and Medicine, University of Utah College of Medicine, and the U. S. Veterans Administration Hospital, Salt Lake City, Utah. This investigation was aided by research grants from the National Institutes of Health, Public Health Service and the Smith, Kline & French Labs. Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

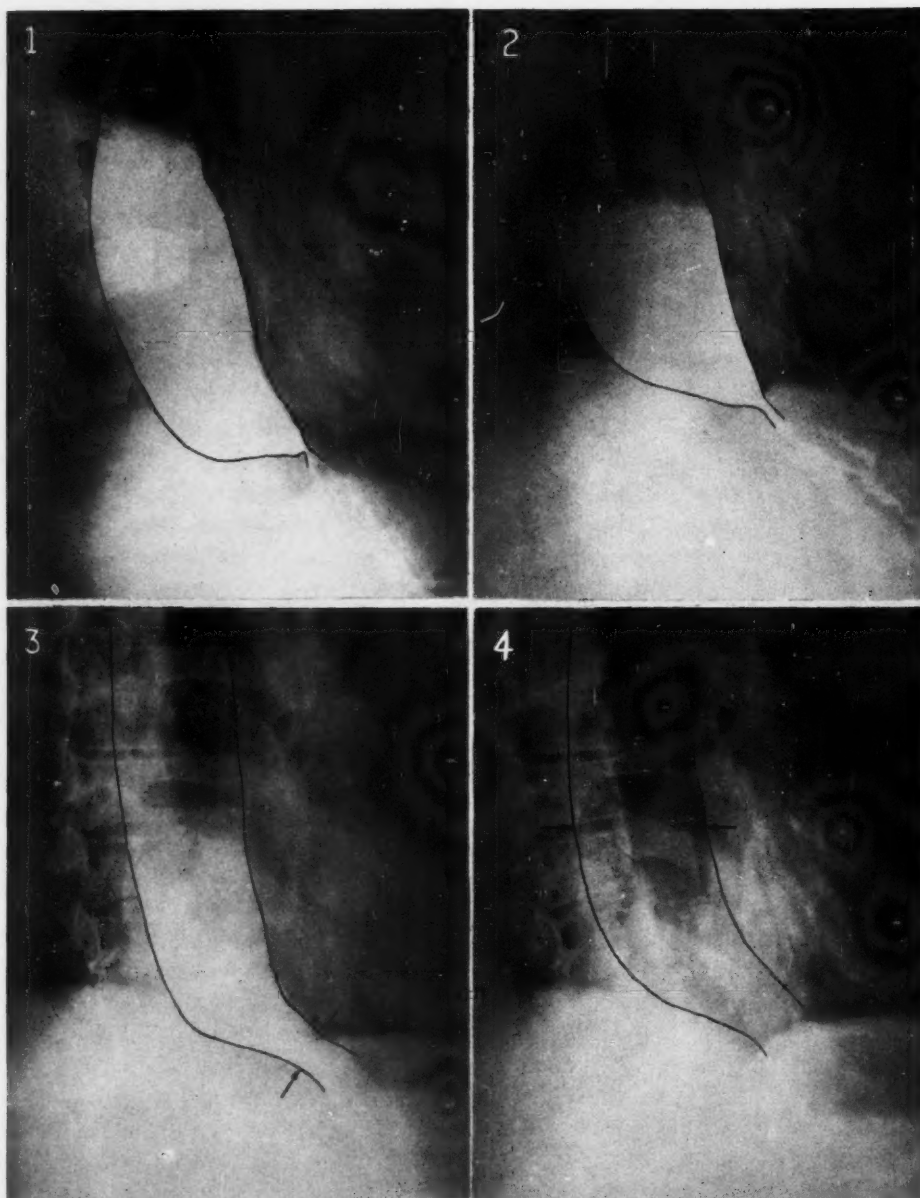


FIG. 1. Pretreatment roentgenogram taken shortly after administration of barium showing dilatation of the lower esophagus and a smooth constriction of the cardioesophageal junction. (The esophagus has been outlined in black in all figures to facilitate reproduction.)

FIG. 2. Pretreatment roentgenogram taken five hours after Figure 1 without additional administration of barium; note the very slow emptying of the esophagus.

FIG. 3. Roentgenogram taken fifteen seconds after administration of barium and three hours after dibenamine.[®] Arrows indicate the narrowest part of the cardioesophageal orifice; note the complete relaxation.

FIG. 4. Roentgenogram taken three minutes after Figure 3; the barium has completely left the esophagus except for a thin film outlining the dilated organ.

topical anesthesia revealed a tight cardioesophageal junction and considerable difficulty was experienced in passing No. 12 and No. 14 bougies into the stomach. Biopsy of the constricted area was reported as gastric mucosa.

The patient was first given tincture of belladonna without relief. On February 1st 500 mg. of dibenamine[®] in 500 cc. of 0.9 per cent NaCl

solution were administered intravenously over a period of one hour. This resulted in marked orthostatic hypotension which gradually disappeared over a period of two days but no significant change in the recumbent blood pressure occurred. Three hours after the infusion of dibenamine[®] fluoroscopy during the administration of barium revealed the cardia to be

relaxed and the barium passed into the stomach through an opening at least 2 cm. in diameter. (Fig. 3.) The esophagus was entirely empty within three minutes. (Fig. 4.) Examination eighteen hours later demonstrated somewhat less complete relaxation of the cardia than that observed shortly after the dibenamine® administration. However, emptying of the esophagus at this time was much more rapid than prior to the dibenamine®. The symptoms of substernal pressure and fullness were almost completely relieved for a period of three or four days. Dibenamine® administration was repeated six days later and again resulted in three days of symptomatic relief; roentgenographic observation revealed no retention of barium in the esophagus. The orthostatic hypotension induced by dibenamine® was less severe after the second administration. Again on March 1st, 350 mg. of dibenamine® were administered prior to esophagoscopy performed under topical anesthesia. The examination disclosed a relaxed cardia and No. 12 to No. 16 bougies were easily passed into the stomach. No persistent relief was provided by this "dilatation" of the relaxed cardia.

Between the second and third administrations of dibenamine® 200 mg. of tetraethylammonium chloride were administered intravenously. Although a significant orthostatic hypotension resulted, roentgenographic examination failed to reveal any relaxation of the cardia and almost all the ingested barium was still present in the esophagus after one hour. The patient received no symptomatic relief from this treatment.

A subsequent attempt at dilatation with a mercury-filled bag, under general anesthesia, was unsuccessful because of difficulty in keeping the bag in position. On April 5th a modified Finney type cardioplasty was performed. The cardiac orifice was found to be very small and tight but it expanded readily as soon as the circular muscle fibers in this area were cut. The patient had an uneventful postoperative course and roentgenographic examination three months later revealed that the lower esophagus was reduced to about one-half its preoperative diameter.

COMMENTS

Although considerable work and speculation have been expended on the subject, the pathologic physiology of cardiospasm is still not clearly established. The "sphincter" at the gastroesophageal junction is poorly defined anatomically and its localized hypertrophy in this condition

is not characteristic. These facts have led various workers to consider primary dilatation,¹ pressure from the liver² or a sphincter action of the diaphragm³ as the precipitating factor. However, obstruction due to constriction by the circular muscle layer of the lower end of the esophagus is now generally accepted as the factor immediately precipitating retention.

Under certain conditions stimulation of the vagi may induce constriction of the lower esophagus in dogs and cats.^{4,5} However, the more prominent response to stimulation of the vagi is relaxation of the gastroesophageal junction. This may be a direct effect or an enteric reflex response to esophageal constriction. Dilatation of the esophagus with a balloon is known to produce reflex relaxation of the cardia in unanesthetized dogs.⁶

It has been known since 1838 and repeatedly confirmed that section of both vagi will produce a condition very similar to cardiospasm,⁷⁻¹⁰ and cardiospasm has been noted as a complication of vagotomy in humans.¹¹ However, constriction does not develop after both the vagal and sympathetic innervations of this region are resected.¹² Electrical stimulation of the lower thoracic sympathetic chain or of the sympathetic fibers along the celiac axis and left gastric artery causes constriction of the gastroesophageal junction in dogs and cats,^{4,12} as does systemic or close intra-arterial injection of epinephrine.⁴ In man spinal anesthesia¹³ or paravertebral sympathetic blockade with local anesthetic agents¹⁴ may relax the cardia in at least certain cases of cardiospasm. Attempts have been made to treat cardiospasm by means of sympathectomy¹⁴⁻¹⁶ but the results have been largely disappointing; perhaps because the operation usually performed does not adequately eliminate the sympathetic innervation of the cardia.^{14,17}

The cardioesophageal junction area thus appears to be a physiologic unit which responds to sympathetic and vagal nerve impulses in much the same manner as other gastrointestinal sphincters. The increased tone (failure to relax) in cardiospasm is apparently due to relative overactivity of the sympathetic (constrictor) control. However, it is still not clear whether this is the result of absolute overactivity, such as might be expected to result from reflex stimulation of the sympathetic nerves in cases precipitated by irritative processes or psychic factors,^{1,18} or a result of a decrease in the inhibitory activity of the vagi or intramural plexus. Degeneration of the intramural ganglia in this

region has been noted in a number of cases of cardiospasm.^{19,20} It is quite probable that the precipitating factor may vary from one case to another, but with the common end result of producing a relative preponderance of sympathetically mediated constriction of the circular muscle layer.

Dibenamine® is the most effective adrenergic blocking agent now available for clinical use. It readily blocks excitatory responses of smooth muscle and gland cells to adrenergic stimuli but it does not alter inhibitory responses or directly stimulate or depress smooth muscle when administered in therapeutic doses.^{21,22} Consequently if absolute or relative sympathetic overactivity is responsible for occlusion of the lower esophagus in cardiospasm, dibenamine® should provide relaxation and relief of the obstruction. That this is indeed the situation, at least in some instances, is indicated by the marked relaxation of the cardia induced by this agent in the case herein reported. The relatively prolonged relief observed after each injection of dibenamine® is probably due to the prolonged adrenergic blocking action characteristic of this agent and its congeners.²¹⁻²³

The ergot alkaloids have also been reported to provide some relaxation of experimental and clinical cardiospasm^{4,24} but the clinical studies with this agent have been complicated by the simultaneous administration of other therapeutic agents. In addition, the doses of ergot administered were probably inadequate to produce significant adrenergic blockade.

Failure of tetraethylammonium to provide relaxation comparable to that induced by dibenamine® in the present case may be related to two factors: (1) incomplete blockade of sympathetic ganglia by the dose administered and (2) the fact that tetraethylammonium inhibits the activity of both the sympathetic and parasympathetic nervous systems. Consequently this agent, in doses short of those required to produce a complete blockade, might fail to alter the balance between the two divisions of the autonomic system.

Mechanical dilatation of the cardia during the period of dibenamine® relaxation failed to provide any improvement in the condition of the patient described herein. This observation is in agreement with the results of the anatomic studies of Lendrum²⁰ who concluded that actual rupture of the spastic circular muscle layer is an important feature of therapeutically effective dilatation.

The administration of adequate blocking doses of dibenamine® induces marked orthostatic hypotension. This cannot properly be considered as a side effect as it is physiologically impossible to produce an extensive, acute blockade of the sympathetic nervous system without impairment of postural reflexes. However, the postural hypotension in the present case was significantly less following the second administration within a period of one week. Reduction in the orthostatic hypotension induced by dibenamine® is probably due to the same factors which rather quickly ameliorate the orthostatic hypotension resulting from extensive surgical sympathectomy. The mechanism of this compensation is poorly understood but it is clear that the vascular system in both animals and man may maintain relatively normal circulation in the absence of sympathetic nervous system control.²⁵ This compensation has been noted to occur much more rapidly after dibenamine® blockade in children²⁶ and would probably be more complete if a continuous blockade were maintained, a possibility which deserves further investigation.

Even temporary blockade with dibenamine® or a related compound may provide a useful tool in differentiating cardiospasm from organic lesions of the lower esophagus and cardia. However, the present necessity for slow intravenous administration of these agents precludes their use as maintenance therapy in cardiospasm. A very large number of congeners of dibenamine® have now been synthesized and studied pharmacologically^{22,23,27} and it appears probable that one or more of these will prove to be sufficiently well absorbed after oral administration to allow for safe and efficient chronic medication. In anticipation of the introduction of an orally effective adrenergic blocking agent into clinical practice it is important to know whether most or only a small percentage of cases of cardiospasm will respond favorably to adrenergic blockade. It is hoped that other workers, with larger series of cases available for study, may provide a reliable answer to this question.

SUMMARY

Administration of dibenamine®* provided marked and prolonged relaxation of the gastroesophageal junction and rapid emptying of the

* The dibenamine® used in these studies was supplied by Dr. William Gump, Givaudan-Delawanna, Inc., N. J. Dibenamine is now distributed for investigational use by the Smith, Kline & French Labs., Philadelphia, Pa.

esophagus in a case of cardiospasm. This observation provides confirmation of previous suggestions that relative or absolute sympathetic overactivity is responsible for this condition. It also points to effective medical therapy of cardiospasm as soon as orally effective congeners of dibenamine® become available for clinical use. However, more extensive studies are still necessary to determine the incidence of favorable responses and the results of more prolonged periods of blockade.

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Effect of Cortisone and ACTH on the Histopathology of Rheumatic Carditis*

Report of a Necropsied Case

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REPORTS vary as to the efficacy of cortisone and ACTH therapy in arresting or altering the carditis of acute rheumatic fever. The ultimate judgment will depend on evaluation of a large scale and long range follow-up of cortisone- and ACTH-treated patients with acute rheumatic fever. Important information may also be obtained, however, from necropsy material from patients dying shortly after or during such therapy. This latter approach will of necessity be limited to cases that have shown a clinically unsatisfactory response. Nevertheless, collection and evaluation of such reports may aid in arriving at valid conclusions concerning the effect of cortisone on the carditis of acute rheumatic fever. It is for this reason that the following necropsied case is reported:

CASE REPORT

A fourteen year old white male was admitted to Grasslands Hospital on December 23, 1950, with fever and dyspnea. The past history was negative with the exception of an allergy for fish and feathers. The patient first became ill in January, 1948, with an upper respiratory infection which lasted two weeks; he recovered uneventfully. In September, 1948, he was noted to have a heart murmur. He remained in good health under medical supervision until June, 1950. Another respiratory infection developed followed a few days later with migratory arthralgia and anemia. At that time the erythrocyte sedimentation rate (Wintrobe) was 29, and the electrocardiogram showed a first degree heart block. He was kept in bed and later was hospitalized in September when he ran a continuous fever and dyspnea. He never showed arthralgia or evidence of heart failure. He was

then transferred to Irvington House on November 8, 1950, for further treatment. At that time there was a systolic thrill at the apex; the PMI was in the anterior axillary line; the rhythm was regular; the second pulmonary sound was louder than the second aortic sound. There was a long blowing systolic murmur at the apex transmitted to the axilla. There was a diastolic murmur along the left sternal border and a questionable systolic murmur at the apex. The blood pressure was 150 systolic and 80 diastolic. The liver edge was at the costal margin. The erythrocyte sedimentation rate (Wintrobe) was 23 mm. per hour. The hematocrit was 41.5 and the hemoglobin 13.5. The red blood cell count was 5,690,000 and the white blood cell count 11,850. Throat cultures were negative for hemolytic streptococci. Seven days later pharyngitis developed but cultures were still negative for streptococci. Two days later his temperature rose and he complained of precordial pain and dyspnea. An electrocardiogram suggested a pericardial reaction. The heart sounds were unchanged. The lungs were clear and the liver was not enlarged. There was no edema and the blood culture was negative. Cortisone therapy was started (100 mg. daily, which was increased to 200 mg. for thirteen days). At the same time he received digoxin, a penicillin preparation (duracillin) and aspirin. Temperature gradually fell from 105°F. in six days to 100°F. but remained elevated at 100 to 101°F. The white blood cell count varied between 22,150 and 48,100. The erythrocyte sedimentation rate (Wintrobe) remained at about 21 mm. per hour. A gallop later developed and a friction rub became audible. He was given mercurial diuretics.

* From The Division of Pathology, Grasslands Hospital and The Department of Laboratories and Research of Westchester County, Valhalla, N. Y.

On December 5, 1950, the non-protein nitrogen was 42, serum sodium was 300 mg. per cent, potassium was 20.5 mg. per cent and the total serum protein was 7.5 gm. per cent. Cortisone was withdrawn. The temperature remained normal on aspirin therapy. The pulse rate varied between 100 and 120. From December 10th the patient showed progressive deterioration; the liver enlarged; vomiting occurred and dyspnea increased. There were basal rales but no peripheral edema. On December 16, 1950, ACTH was started (using 60 mg. and increasing to 300 mg. daily) and discontinued on December 23rd. Icterus appeared on December 21st and the serum bilirubin was 3.2 mg. to 4.7 mg. on December 19th. The non-protein nitrogen was 100 mg. and albuminuria was present. Twenty-four-hour urine output fell from 700 to 1,675 to 375 to 980 cc. The patient was transferred to Grasslands Hospital for further treatment.

The significant physical findings on admission to Grasslands Hospital were as follows: Temperature was 98.4°F., pulse rate 130, respirations 40 and blood pressure 145/0. The skin was dry and there were petechiae on the trunk. The lungs were clear. The PMI was in the 7th intercostal space at the anterior axillary line. There was a palpable systolic thrill at the apex, the rate was regular and there was a loud blowing systolic murmur and a rumbling diastolic murmur at the apex. There was also an aortic systolic murmur. The second pulmonic sound was louder than the aortic sound and a gallop was heard over the pulmonic area. The sounds were of good quality, the liver was enlarged and tender. There was no edema or swelling but all four extremities were painful. The red blood cell count was 4,000,000, hemoglobin 11 gm. and the white blood cell count 17,750 with 88 per cent polymorphonuclear leukocytes. Urine contained 4 plus albumin. Two blood cultures were negative. Chest x-ray picture showed enlarged globular heart. There was an accentuation of the vascular pattern of both hilar regions. The electrocardiogram showed myocardial changes and a prolonged A-V conduction time. The patient expired one day after admission.

At necropsy the following were found: Grossly, the body was that of a fourteen year old while male measuring 66 inches in length and weighing about 135 pounds. No definite icterus could be seen. The extremities showed no unusual features and there was abundant subcutaneous panniculus and a well developed

musculature. The pericardial cavity was almost obliterated by fibrous and fibrinous adhesions. The pleural cavities contained about 200 cc. of serous colored fluid each and the pleural surfaces were smooth and glistening. The peritoneal cavity contained no fluid but there were areas of

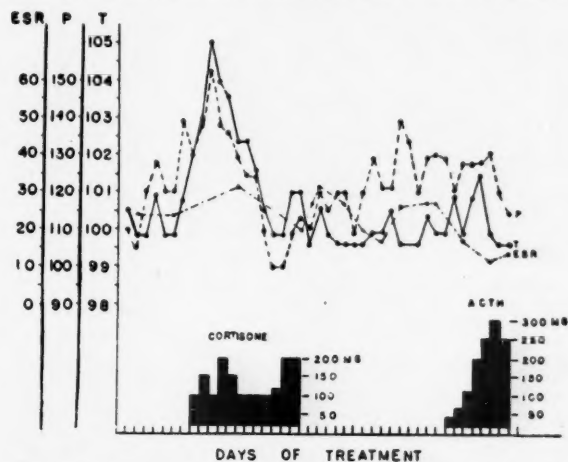


Fig. 1. Schematic presentation of cortisone and ACTH therapy and the pulse, temperature and sedimentation rate response.

petechial hemorrhage over the parietal peritoneum and the mesentery. The lower edge of the liver was seen 4 cm. below the right costal region.

The heart weighed 525 gm. and was extremely flaccid, tending to lose its shape when lying upon the table. The epicardial surface was deeply congested and covered with fibrous adhesions and fibrinous exudate. There were petechial hemorrhages over the surface. The right auricle was dilated but the endocardium was smooth. The tricuspid valve was not remarkable; the right ventricle was dilated and atrophied; its wall averaged 0.75 cm. in thickness. The pulmonic valve was not remarkable. The left auricle and auricular appendage showed no unusual features. The mitral valve was anatomically incompetent and the anterior mitral leaflet was thickened particularly at its free margin. Along this free margin of the mitral valve leaflet there was a row of small 1 mm. sized pale tan verrucae. The chordae tendineae were shortened, thickened and also contained some verrucae on the endocardial surfaces. The papillary muscles were hypertrophied. The left ventricle wall measured in thickness up to 1.5 cm. The aortic valve was competent, its leaflets were thin but showed a slight thickening at their free edges; there was no fusion at the commissures. The coronary ostae were patent

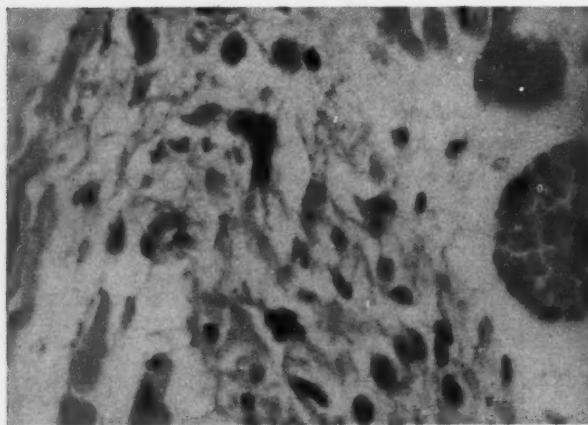


FIG. 2. Photomicrograph showing typical Aschoff nodule; (hematoxylin and eosin, high power).

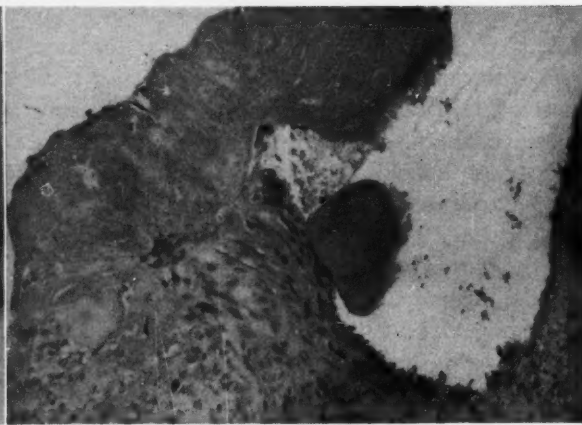


FIG. 3. Photomicrograph showing typical verrucae on the mitral valve; (hematoxylin and eosin, high power).

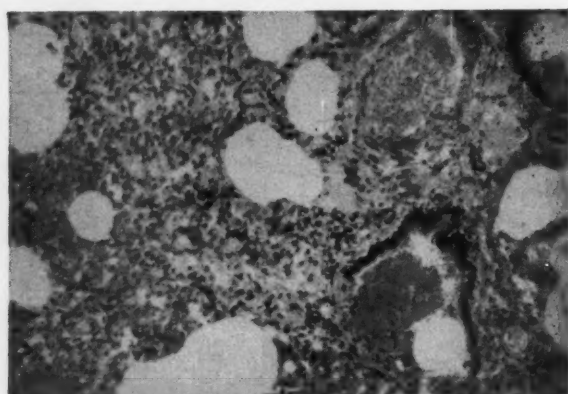


FIG. 4. Photomicrograph showing dense interstitial infiltration of the lungs with mononuclear cells; (hematoxylin and eosin, high power).

and the coronary arteries revealed a minimal degree of atheromatosis. The myocardium was pale, soft and contained areas of mottling and congestion.

There was congestion of the mucous membranes of larynx, trachea and bronchi. The right lung was voluminous and weighed 800 gm. On section it presented a homogeneous, firm surface that was densely congested and mottled. The intrapulmonary arteries and bronchi were not remarkable. The left lung weighed 650 gm. and was similar in appearance to the right. The spleen weighed 200 gm., was firm and the pulp was purple. The liver weighed 1,250 gm. and on section was mottled yellowish to red with a distinct tendency towards a nutmeg appearance.

The adrenals were of usual size, shape and position. The right adrenal weighed 5½ gm. and the left 6½ gm. On section the cortex appeared to be of usual thickness and the medulla was not remarkable. The other organs

including the brain and the pituitary gland did not reveal any significant gross changes.

Microscopic examination of the heart revealed the myocardial fibers were hypertrophied. The intramyocardial arterioles displayed thickened intimas. A few Aschoff nodules were seen. These were of the usual appearance and contained acidophilic (fibrinoid) material. The endocardium was thickened and the mitral valve was fibrotic, diffusely infiltrated with inflammatory cells and vascularized. There were areas of acidophilic (fibrinoid) change in the collagen and one large nodule showing such change was located on the surface of the valve just beneath the endocardium. Adhering to it was a fibrinoid verruca and scattered about it were lymphocytes, myocytes and fibroblasts. The epicardium was covered by a thick layer of granulation tissue, surrounding which there was abundant fibrin. The media of the aorta was edematous.

In the lungs there was a diffuse infiltration of the alveolar septa and to a lesser degree of the alveolar sacs by large mononuclear cells. Moderate amounts of edema fluid were present in some alveoli while others were emphysematous. The blood vessel walls were somewhat thickened and the blood vessels were engorged. There was hemorrhage in some alveoli and bronchial lumens. Erythrophagocytosis was noted in many alveolar septa. In the spleen the follicles were prominent and the sinuses were engorged with blood. There was hyperplasia of the reticulum cells. In the liver there was marked central congestion and vacuolization of the peri-efferent vein liver cells. The liver cells in the periportal area were not remarkable. Inspis-

sated bile was seen between the liver cords in the central regions. In the adrenals there was moderate depletion of cortical lipoid and marked interstitial congestion. There was no atrophy or hyperplasia. The other organs did not reveal significant microscopic findings.

The final anatomic diagnoses were rheumatic pericarditis, myocarditis and endocarditis of mitral valve; hypertrophy and dilation of the heart; interstitial pneumonitis, bilateral; congestion of viscera and fatty change of liver.

COMMENTS

This patient cannot be considered to have shown any significant clinical response to cortisone and ACTH therapy. However, there was a drop in the temperature and in the pulse rate during the cortisone phase of treatment. (Fig. 1.) The characteristic lesions of rheumatic pancarditis such as Aschoff's nodules, verrucae and interstitial valvulitis, auricular endocarditis and fibrinous pericarditis were all present. There was no alteration in the histopathologic appearance of these lesions as compared with that seen in typical non-cortisone treated patients. (Figs. 2 and 3.) The Aschoff nodules con-

tained the usual number and type of cells along with the eosinophilic necrosis of collagen. The verrucae on the mitral valve also showed no deviation in appearance from those seen in other cases of rheumatic endocarditis. The exudate on the pericardium contained abundant fibrin and the granulation tissue was rich in fibroblasts.

The lungs (Fig. 4) were the site of a widespread infiltration of mononuclear cells. The picture in the lungs was compatible with what has been referred to by many as rheumatic pneumonia. It is interesting to note that in spite of cortisone therapy mononuclear cell infiltration was dense and diffuse.

SUMMARY

A necropsied case of cortisone- and ACTH-treated acute rheumatic carditis is presented. The characteristic lesions of rheumatic carditis were present and revealed no deviation from the changes usually seen in non-cortisone treated patients with rheumatic carditis.

Acknowledgment: We wish to thank Dr. Harold C. Anderson of Irvington House for permission to use clinical abstract in this case.

Book Review

Personality in Peptic Ulcer. A. J. Sullivan, M.D., and T. E. McKell, M.D. Springfield, Ill., 1950. Charles C Thomas. Price \$3.00.

With the increasing complexities of modern medicine any general review of a major clinical problem is always a welcome addition to the medical literature. This is especially applicable to this small volume on "Personality in Peptic Ulcer," because of the increasing incidence of peptic ulcer in our civilization. With the recent tendency to solve the clinical problem of ulcer by means of surgical resection or vagotomy, a re-emphasis of the total personality involvement in this disorder should enable the general physician to plan a more rational total therapy.

The authors, on the basis of 200 ulcer cases at the Ochsner Clinic, review their clinical and psychologic findings in light of recent psychosomatic investigations. They find that a peptic ulcer personality profile does exist and that 70 per cent of their cases are characterized by their intense drive, job versatility, excessive self-reliance and excessive sense of responsibility. These various traits of the "typical ulcer patient" are amusingly illustrated by a series of excellent cartoons that should help to re-emphasize the importance of these features in most ulcer individuals. They strongly disagree with Alexander's hypothesis (that the active independent drives of an ulcer individual are the reaction to repressed unconscious oral-receptive and dependent needs) as to the etiology of these active drives. The authors believe that Alexander's formulation applies to only 10 per cent of their cases. In place of Alexander's craving for dependency they would substitute the Adlerian craving for superiority. This, they believe, is the essential driving force of the ulcer individual. Apart from a review of other pertinent psychiatric and psychosomatic findings, they briefly stress the therapeutic importance of a psychologic and medical prophylactic attitude in the treatment of peptic ulcer.

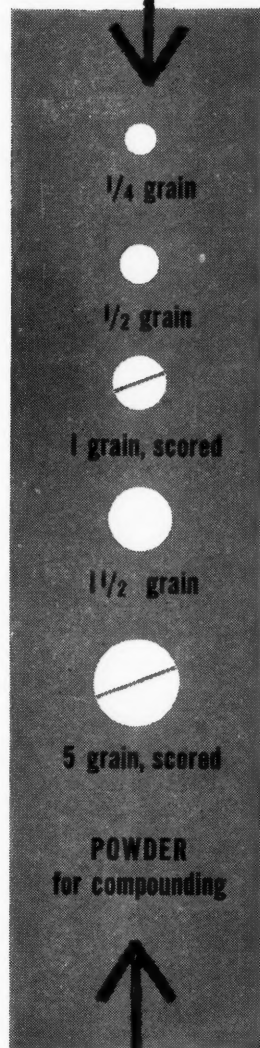
The authors make several methodologic errors in their consideration of the psychodynamic

factors. Alexander's formulations were based on nine psychoanalytic cases. It should be evident that psychologic data obtained by an interview technic cannot prove nor disprove data obtained by a detailed psychoanalytic technic. This does not mean that the authors' general psychologic data are not valid or useful. Alexander's formulations can be further validated or disproved only by similar intensive psychologic studies. The general applicability of these findings to the "general ulcer population" must await the detailed study of a statistically significant sample of the ulcer population. The authors also appear to overstress the Alexander hypothesis as the major psychodynamic formulation in the psychosomatic literature. Mittelman's Rage and Hostility Hypothesis seems to be an equally useful one. The Adlerian craving for superiority as the dominant motive force behind the excessive drive of the ulcer individual is a possible theoretical construct. Its validity, however, must await scientific proof that it is a primary drive and not a secondary reaction to various psychic conflicts.

At the present state of our psychosomatic knowledge of peptic ulcer it is clear that none of the formulations fully explains the causation of ulceration in all individuals. It can, however, be definitely stated that in the majority of cases of peptic ulcer the gastric dysfunction and ulceration is a physiologic concomitant reaction of various psychic states of tension and conflict. The choice of the stomach as the site for this dysfunction is, to date, an unsolved problem. This organ specificity may turn out to be psychologically, genetically or physiologically determined. In spite of the many unsolved problems there is a great deal of psychodynamic data that can be beneficially applied in the total treatment of ulcer individuals. This useful little volume would have accomplished its purpose if it encourages the general physician as well as the gastroenterologist to help the ulcer individual resolve his emotional problems by brief or intensive psychotherapeutic means.

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1. Lowsley, O. S., and Kirwin, T. J.: *Clinical Urology*. Baltimore, Williams & Wilkins Company, 1944; vol. 1, p. 939.

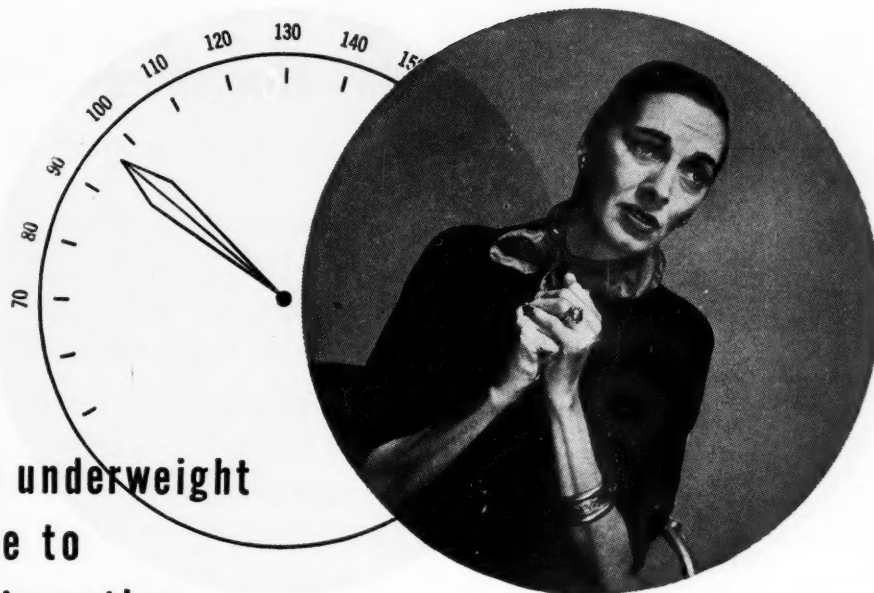


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- Ref.: 1. Becker, G.H., et al.: *Gastroenterology* 14:80, 1950
 2. Jones, C.M., et al.: *Ann. Int. Med.* 29:1, 1948
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 4. Kiefer, E.D. & Arnold, W.T.: *J.A.M.A.* 144:903 (Mar. 11) 1950

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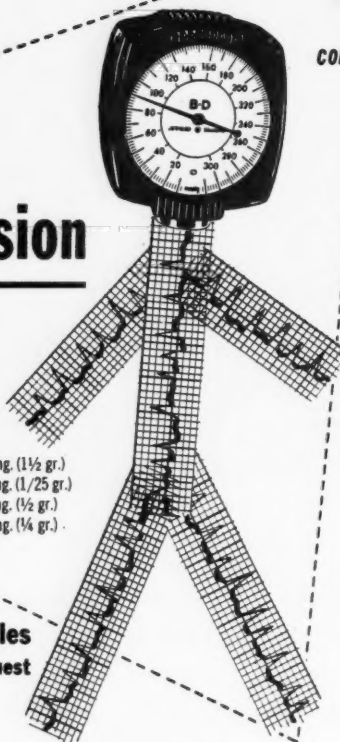
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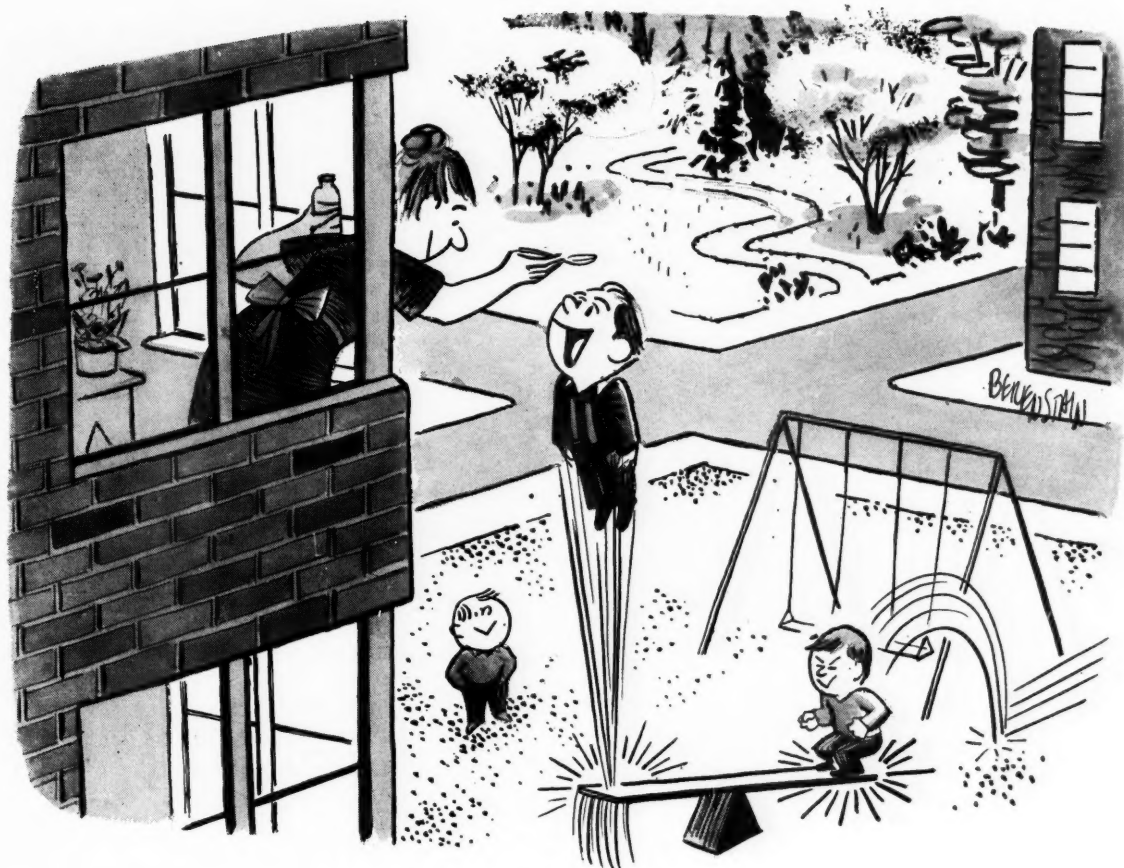
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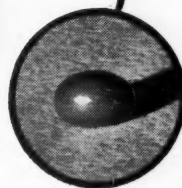
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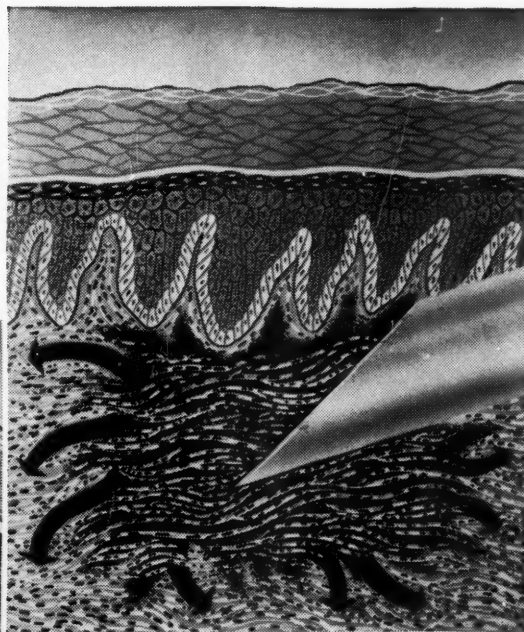
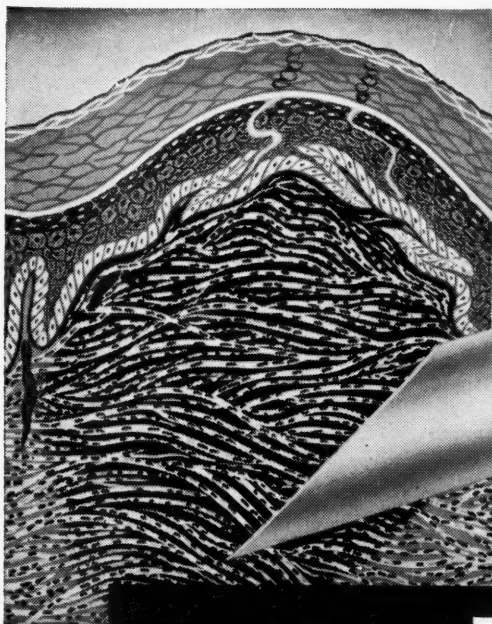
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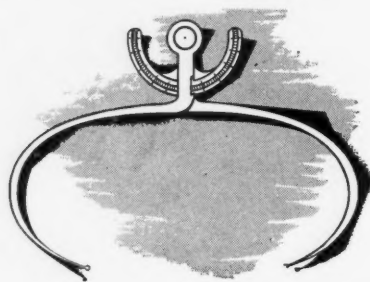
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